QT PROLONGING PHARMACOTHERAPY IN OLDER ADULTS RECEIVING HOME CARE

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Tiivistelmä/Referat – Abstract

Many drugs are associated with the risk of QT prolongation and torsades de pointes (TdP). The risk increases with other risks factors for QT prolongation. Recognizing risk factors and QT prolonging drugs is critical in the management of this drug-related problem. The aim of this master's thesis was to study the prevalence of use of QT prolonging drugs in older adults receiving home care. Additionally, the aim was to study concomitant use of QT prolonging drugs as well as clinically significant QT prolonging drug-drug interactions in the participants. The secondary objective was to study the most commonly used QT prolonging in the participants.

The material used in this master's thesis originated from a randomized controlled trial in City of Lohja, Finland, which enhanced a coordination in medication risk management for older home care clients. The analysis of the baseline data collected in fall 2015 was only deepened regarding QT prolonging drugs. The participants (n=188) were older adults (≥65 years) receiving regular home care from City of Lohja, randomized into an intervention group (n=101) and a control group (n=87). The majority of the participants were women (69%). The mean age of the participants was 83 years. Data on the participants' drugs were collected from their medication lists. Clinically significant drug-drug interactions were identified using the SFINX database. The QTDrugs Lists of CredibleMeds were used for identifying drugs associated with QT prolongation and TdP.

On average, the participants (n=188) used 2.3 drugs (SD 1.3, median 2.0) associated with QT prolongation and TdP. Of the participants, 36% (n=67) used drugs with known risk of TdP (QTDrugs List 1). The most commonly used drugs with known risk of TdP were donepezil and citalopram. The prevalence of QTDrugs List 2 drugs (possible risk of TdP) was 36% (n=67). Most of the participants (n=156, 83%) used drugs which under certain circumstances are associated with TdP (QTDrugs List 3). One fifth (21%) of the participants used concomitantly 2-3 drugs associated with QT prolongation and TdP. QT prolonging drug-drug interactions (SFINX-D interactions) were found in 3% of the participants. The drugs involved in the drug-drug interactions were donepezil, (es)citalopram and haloperidol.

The prevalence of use of clinically relevant QT prolonging drugs (QTDrugs Lists 1-2) was higher in this study compared with the prevalence in outpatients in previous studies. Concomitant use of QT prolonging drugs is common in outpatients. Health care professionals need to be educated on the risks of QT prolongation, TdP and the risks of using QT prolonging drugs concomitantly. Risk assessment tools considering patient-specific risk factors could be more widely used, as they may reduce modifiable risk factors, and actual events of QT prolongation and TdP may be avoided. There is a need for systematic procedures for assessing and managing the risks of QT prolongation and TdP in the Finnish health care system.

Avainsanat – Nyckelord – Keywords

QT prolongation, torsades de pointes, acquired long QT syndrome, pharmacotherapy, older adults, home care, risk management

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Tiivistelmä/Referat – Abstract

Många läkemedel är förknippade med en risk för QT-tidsförlängning och torsades de pointes (TdP). Risken ökar med andra samtidiga riskfaktorer för QT-tidsförlängning. Det är avgörande för hanteringen av detta läkemedelsrelaterade problem att kunna identifiera riskfaktorer och läkemedel som kan förlänga QT-tiden. Syftet med denna pro gradu-avhandling var att studera förekomsten av användning av QT-tidsförlängande läkemedel hos äldre vuxna inom hemvården. Dessutom studerades samtidig användning av QT-tidsförlängande läkemedel samt kliniskt relevanta läkemedelsinteraktioner med risk för QT-tidsförlängning hos deltagarna. Det sekundära syftet var att studera de mest använda QT-tidsförlängande läkemedlen bland deltagarna.

Materialet som användes i den här pro gradu-avhandlingen härrörde sig från en randomiserad kontrollerad interventionsstudie utförd i Lojo, vilken förbättrade en samordnad riskhantering av läkemedel hos äldre hemvårdsklienter. I analysen av det material som insamlats under hösten 2015 låg fokus på QT-tidsförlängande läkemedel. Deltagarna (n=188) var äldre vuxna (≥65 år) som använde hemvårdstjänster regelbundet i Lojo, randomiserade till en interventionsgrupp (n=101) och en kontrollgrupp (n=87). Majoriteten av deltagarna var kvinnor (69 %). Deltagarnas medelålder var 83 år. Från deltagarnas läkemedelslistor samlades in uppgifter om använda läkemedel. Från databasen SFINX identifierades kliniskt relevanta läkemedelsinteraktioner. Listor över QT-tidsförlängande läkemedel från CredibleMeds användes för att identifiera läkemedel associerade med QT-tidsförlängning och TdP.

Deltagarna (n=188) använde i genomsnitt 2,3 läkemedel associerade med QT-tidsförlängning och TdP (standardavvikelse 1,3; medianvärde 2,0). Av deltagarna använde 36 % (n=67) läkemedel med känd risk för TdP ("QTDrugs List 1"). De mest använda läkemedlen med känd risk för TdP var donepezil och citalopram. Förekomsten av läkemedel med möjlig risk för TdP ("QTDrugs List 2") var 36 % (n=67). De flesta deltagare (n=156, 83 %) använde läkemedel som under vissa omständigheter är associerade med TdP (”QTDrugs List 3”). En femtedel (21%) av deltagarna använde 2–3 QT-tidsförlängande läkemedel samtidigt. Läkemedelsinteraktioner (SFINX-D interaktioner) som kan leda till QT-tidsförlängning hittades hos 3 % av deltagarna. De läkemedel som var involverade i läkemedelsinteraktionerna var donepezil, (es)citalopram och haloperidol.

Förekomsten av användning av kliniskt relevanta QT-tidsförlängande läkemedel ("QTDrugs Lists 1–2") var högre i denna studie jämfört med förekomsten hos patienter inom öppenvården från tidigare studier. Samtidig användning av flera QT-tidsförlängande läkemedel hos patienter inom öppenvården är vanlig. Hälso- och sjukvårdspersonal behöver utbildas om riskerna för QT-tidsförlängning, TdP och om riskerna av samtidig användning av QT-tidsförlängande läkemedel. Riskbedömningsverktyg som tar hänsyn till patientspecifika riskfaktorer kunde användas i en större utsträckning, eftersom användningen av dessa kan minska på modifierbara riskfaktorer och faktiska händelser av QT-tidsförlängning och TdP kan undvikas. Det finns ett behov av systematiska rutiner för bedömning och hantering av risken för QT-tidsförlängning och TdP i det finska hälsovårdssystemet.

Avainsanat – Nyckelord – Keywords

QT-tidsförlängning, torsades de pointes, förvärvat långt QT syndrom, läkemedelsbehandling, äldre vuxna, hemvård, riskhantering

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LIST OF ABBREVIATIONS

ADE	Adverse drug event
ACC	American College of Cardiology
AHA	American Heart Association
aLQTS	Acquired long QT syndrome
AZCERT	Arizona Center for Education and Research on Therapeutics
bpm	Beats per minute
CDSS	Clinical decision support system
cLQTS	Congenital long QT syndrome
CPOE	Computerized physician order entry
CYP	Cytochrome P450 enzyme
DDI	Drug-drug interaction
diLQTS	Drug-induced long QT syndrome
DRP	Drug-related problem
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ECG	Electrocardiogram
ESC	European Society of Cardiology
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
$I_{Ca\text{-}L}$	L-type calcium current
I_K	Potassium current
I_{K1}	Inwardly rectifying potassium current
I_{Kr}	Rapidly activating delayed rectifier potassium current
I_{Ks}	Slowly activating delayed rectifier potassium current
I_{Ku}	Ultra rapidly activating delayed rectifier potassium current
I_{Na}	Depolarizing sodium current
I_{t0}	Transient outward potassium current
LQTS	Long QT syndrome
PHARAO	Pharmacological Risk Assessment Online
RCT	Randomized controlled trial
SD	Standard deviation

SFINX	Swedish, Finnish Interaction X-referencing
TdP	Torsades de pointes
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WHO	World Health Organization

DEFINITIONS

Action potential

Voltage changes generated across the membrane of a nerve or muscle cells when the cell is activated through a variety of stimuli (electrical, chemical, mechanical) (Khan 2006).

Cardioversion

The procedure of converting an abnormal heart rhythm (e.g. ventricular tachycardia with pulse, supraventricular tachycardias, including atrial arrhythmias) to a normal sinus rhythm (Shea and Maisel 2002; Ong et al. 2016) Cardioversion may be chemical or electrical (Shea and Maisel 2002). Chemical cardioversion means administering antiarrhythmic drugs (intravenously or orally) to restore the heart rhythm. In electrical cardioversion, also known as direct-current cardioversion, a synchronized electrical current is delivered through the chest wall to the heart while the patient is sedated. The current causes all heart cells to contract simultaneously, thus interrupting and terminating the abnormal rhythm. By this definition, cardioversion is not as urgent of a procedure as defibrillation as the patients are not in cardiac arrest (Ong et al. 2016).

Defibrillation

Termination of ventricular fibrillation or pulseless ventricular tachycardia by electricity (Ong et al. 2016). By using electrical shock to depolarize the myocardium coordinated contractions may occur.

Depolarization

The inside of the cell membrane is considered negatively charged and the outside positively charged in the resting period of the cell (Dale 2004). Flow of ions inside and across the cell membrane creates a flow of electricity (and generates signals on an ECG). An electrical impulse in the heart causes an excited state; the inside of the myocytes rapidly becomes positive in relation to the outside, this is called depolarization. Once the myocytes have been depolarized, a second wave of depolarization cannot occur until the first wave of depolarization is finished (absolute refractory period).

Electrocardiogram (ECG)

An electrocardiogram records electrical activity occurring in the heart when it contracts. (Dale 2004). A 12-lead ECG is commonly used. Three standard leads and three augmented leads record electrical activity in the frontal plane and are often placed on wrists and ankles. Six precordial (placed on the chest) leads record electrical activity in the horizontal plane. When combining the electrodes, 12 different views of the same electrical activity are shown on the ECG graph paper, the separate views are called ECG leads.

Older adult

In most developed countries, people ≥65 years of age are considered older adults (World Health Organization 2017). Journal of American Geriatrics Society recommends that authors use the term "older adults" instead of words like aged, elder, elderly or senior when referring to individuals aged ≥65 years (Lundebjerg et al. 2017).

P wave

Demonstrates atrial depolarization on an ECG (Dale 2004).

QRS complex

Demonstrates ventricular depolarization made up of a combination or variation of Q, R and S waves (Dale 2004).

QT interval

The QT interval is described as the time from the beginning of the QRS complex to the end of the T wave on the ECG (Thomas and Behr 2015). The QT interval describes the duration of ventricular depolarization (QRS complex) and repolarization (T wave) (Dale 2004; Thomas and Behr 2015).

Regular home care client

A client using home help services and/or home nursing services based on a valid service- and care plan or a client receiving home care services at least once a week despite not having a service- and care plan (National Institute of Health and Welfare 2018).

Repolarization

The stimulated myocyte is returned to its resting state (Dale 2004). This phase of recovery allows the inside of the cell membrane to return to its normal negative charge. The resting state continues until the arrival of the next wave of depolarization. The relative refractory period occurs during repolarization, at which point the myocyte may be depolarized again but only by a strong stimulus.

RR interval

On an ECG the RR interval is the interval from the onset of one R wave to the onset of the next RR wave (Dale 2004). Heart rate (number of heartbeats in one minute) is measured from the RR interval to determine ventricular rate, and P wave to next P wave to determine atrial rate.

Sinus rhythm

A normal sinus rhythm is the normal rhythm of the heart where an electrical impulse is initiated in the sinoatrial (SA) node, and then travels through the atrioventricular (AV) node and bundle of His, bundle branches and Purkinje fibers (Dale 2004; Landrum 2013) Some of the characteristics of sinus rhythm are:

- RR intervals are regular on the ECG strip
- The P waves (represents atrial depolarization) have a similar and uniform shape. Before each QRS complex (represents ventricular depolarization) there is one P wave
- Equal numbers of P waves and QRS complexes are displayed on the ECG (atrial and ventricular rates are equal)
- Heart rate is 60-100 beats per minute.

T wave

Demonstrates ventricular repolarization on an ECG (Dale 2004).

Ventricular fibrillation

During ventricular fibrillation (VF), the cardiac muscle does not contract rhythmically, only “quivers” (Khan 2006). There is therefore no heartbeat and no blood pumps out of

the heart (cardiac arrest). VF results in sudden faintness, loss of consciousness and cessation of breathing. If the abnormal heart rhythm is not corrected within minutes, death occurs. The state requires cardiopulmonary resuscitation until electrical countershock (defibrillation) can be performed to change the state to normal heartbeats.

Ventricular tachycardia

Ventricular tachycardia is an arrhythmia caused by abnormal electrical activity in the ventricles. This causes the heart to beat faster than normal, usually >100 bpm (Zipes et al. 2006; Raatikainen 2016). Ventricular tachycardia can be divided into clinical subtypes based on the origin of the arrhythmia, the duration and characteristics of the twist of the QRS complex (Zipes et al. 2006; Raatikainen 2016)

- Non-sustained VT: Three or more beats in duration, terminating in less than 30 seconds
- Sustained VT: VT lasts longer than 30s or causes hemodynamic disturbance
- Monomorphic VT: VT with a single QRS morphology
- Polymorphic VT: VT with a changing or multiform QRS morphology
- Torsades de pointes (TdP): a polymorphic VT associated with QT interval prolongation. Electrocardiographically characterized by twisting of the peaks of the QRS complexes around the isoelectric line during the arrhythmia.
- Ventricular flutter: the diastolic phase is not distinguished, no isoelectric interval between successive QRS complexes.
- Ventricular fibrillation

TABLE OF CONTENTS

1 INTRODUCTION

Many drugs, both cardiovascular and non-cardiovascular are associated with the risk of drug-induced QT prolongation and torsades de pointes (TdP) (Woosley et al. 2018b). QT prolongation is a measure of delayed ventricular repolarization. TdP is a rare polymorphic ventricular tachycardia (VT) that can cause reversible syncope. The condition may worsen and lead to fatal ventricular fibrillation (VF) (Thomas and Behr 2015; Schwartz and Woosley 2016). About 200 drugs on the international market are associated with QT interval prolongation and TdP (Woosley et al. 2018b). In addition to QT prolonging drugs, other non-pharmacological risk factors for acquired long QT syndrome (aLQTS) as well as TdP are known (Schwartz and Woosley 2016; Vandael et al. 2017b). Demographic factors such as female sex and age ≥65 years, cardiovascular diseases and electrolyte disturbances are some of the risk factors for QT prolongation. There is an increased risk for TdP in patients with multiple clinically recognizable risk factors (Drew et al. 2010).

Older adults are more prone to QT prolongation and TdP as risk factors increase due to polypharmacy, drug-drug interactions (DDIs), adverse drug events (ADEs) or illness (Kivelä and Räihä 2007; Moreno-Gutiérrez et al. 2016). Older adults also have an impaired ability to compensate for ADEs. Guidelines for management of QT prolongation and TdP recommend that patient-specific risk factors need to be considered and attention should be given especially to high risk patients (Roden 2004; Royal College of Psychiatrists London 2006; Drew et al. 2010). Identifying risk factors that are adjustable may be more relevant than baseline electrocardiogram (ECG) monitoring (Muzyk et al. 2012). Risk assessment tools may identify patients with a higher risk of QT prolongation or TdP for whom further or continuous ECG monitoring or monitoring of serum electrolyte concentration is necessary (Tisdale et al. 2013; Vandael et al. 2017a).

In Finland, each local authority is required to arrange and develop services to support the wellbeing, health and functional capacity of the older citizens (Act on Supporting the Functional Capacity of the Older Population and on Social and Health Services for Older Persons 980/2012). The services should promote older adults to reside in their own homes

independently or with assistance. Regular medication review and avoidance of unnecessary medication can reduce the risk of DDIs and drug-related problems (DRPs) in older adults (Kivelä and Räihä 2007; Leikola et al. 2012). To the thesis author's knowledge, there have not been conducted any Finnish studies focusing on QT prolonging pharmacotherapy in home care clients. Most Finnish studies have focused on the genetics of QT prolongation. Overall, there is a lack of studies conducted on QT prolonging pharmacotherapy in older adults receiving home care internationally, since studies usually focus on inpatient settings. Concomitant use of QT prolonging drugs in in- and outpatient settings is common (Curtis et al. 2003; Sarganas et al. 2014; Tay et al. 2014; Schächtele et al. 2016). There is a need to study QT prolonging pharmacotherapy in outpatients since outpatients may not be as closely monitored as inpatients regarding QT prolongation.

The aim of the master's thesis was to shed light on a serious DRP and to study risk assessment and management of QT prolonging pharmacotherapy. In the empirical part of the master's thesis, QT prolonging drugs used by older adults receiving home care in City of Lohja, Finland were identified using medication lists originating from a randomized controlled trial (RCT) (Toivo et al. 2018a,b). The thesis focused on risk assessment and management of drug-induced QT prolongation. Additionally, there is a short chapter on congenital long QT syndrome (cLQTS) included.

LITERATURE REVIEW

2 INTRODUCTION TO QT INTERVAL PROLONGATION AND TORSADES DE POINTES (TdP)

Occasional syncope and polymorphic ventricular tachycardia (TdP) were observed for the first time while using an antiarrhythmic agent in the 1920s (Roden 2016). The phrase "torsades de pointes" was first defined in 1966 by the French cardiologist François Dessertenne (Dessertenne 1990; Thomas and Behr 2015). The phrase translates to

“twisting of the points” and describes distinct characteristics of the QRS complex on the ECG (Figure 1).

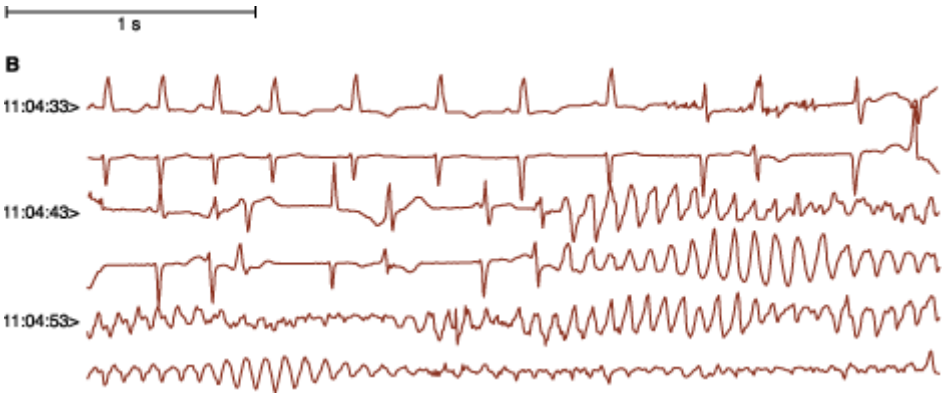

Figure 1. Example of torsades de pointes (Hedman and Hartikainen 2017).

In the 1950s and 1960s, autosomal recessive and dominant forms of cLQTS were reported (Saenen and Vrints 2008; Roden 2016). In the 1970s and 1980s, there were reports on QT prolongation and TdP following pharmacotherapy with drugs other than antiarrhythmics. The drug regulatory authorities began demanding testing of drugs for potential QT prolongation in the 1990s (Schwartz and Woosley 2016). The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has since then published guidelines for clinical evaluation of the potential for QT prolongation by pharmaceuticals, ICH E14, and preclinical testing, ICH S7B (European Medicines Agency 2005a; European Medicines Agency 2005b). Numerous pharmaceuticals have been withdrawn from the market because of adverse events caused by QT prolonging drugs (Schwartz and Woosley 2016). In Finland, several drugs with different indications have been withdrawn in the 1990s and 2000s (Pelkonen and Pasanen 2006; Nurminen 2015). The gastroprokinetic agent cisapride, the antipsychotic agent thioridazine, the antihistamine terfenadine and the antihypertensive mibefradil are examples of drugs withdrawn from the Finnish market.

2.1 Definition of prolonged QT interval

The ECG is a method of evaluating the electrical activity of the heart (Tisdale 2016). The ECG represents the phases of atrial and ventricular action potentials (Figure 2). There are five phases in the cardiac action potential (Morita et al. 2008; van Noord et al. 2010). The P wave represents depolarization and is required for atrial contraction (Tisdale 2016). The QRS complex represents ventricular repolarization (corresponds to phase 0 and phase 1 of the ventricular action potential) and is necessary for ventricular contraction. In phase 0, a rapid inward current of positively charged sodium ions (I_{Na}) depolarizes the ventricle. A rapid transient outward potassium current (I_{t0}) results in early rapid repolarization (phase 1). In Phase 2, the balance of the inward depolarizing calcium current ($_{ICa\text{-}L}$) and outward rectifier potassium currents (I_{Ks} and I_{Kr}) forms a plateau phase. I_{Kr} is encoded by the KCNH2 gene (formerly known as hERG), which is associated with QT prolongation. The T wave represents the final part (phase 3) (Tisdale 2016). In phase 3, late repolarization phase results from efflux of potassium (I_{Kr}, I_{Ku}, I_{Ks}) (Morita et al. 2008; van Noord et al. 2010). In phase 4, the resting potential is maintained by the inward rectifier potassium current (I_{K1}). Ventricular repolarization starts as soon as depolarization in phase 0 ends and is complete at the end of phase 3. Therefore, the QT interval (Figure 2) represents the complete period of ventricular repolarization. If phase 3 becomes prolonged, the left ventricle becomes susceptible to premature electrical impulses, “early afterdepolarizations”. This is shown on the ECG as a prolonged QT interval and this can trigger TdP. A standard 12-lead ECG is generally sufficient for accurate QT interval measurement, i.e. a measurement of delayed ventricular repolarization, and is the most frequently used method (Goldenberg et al. 2006).

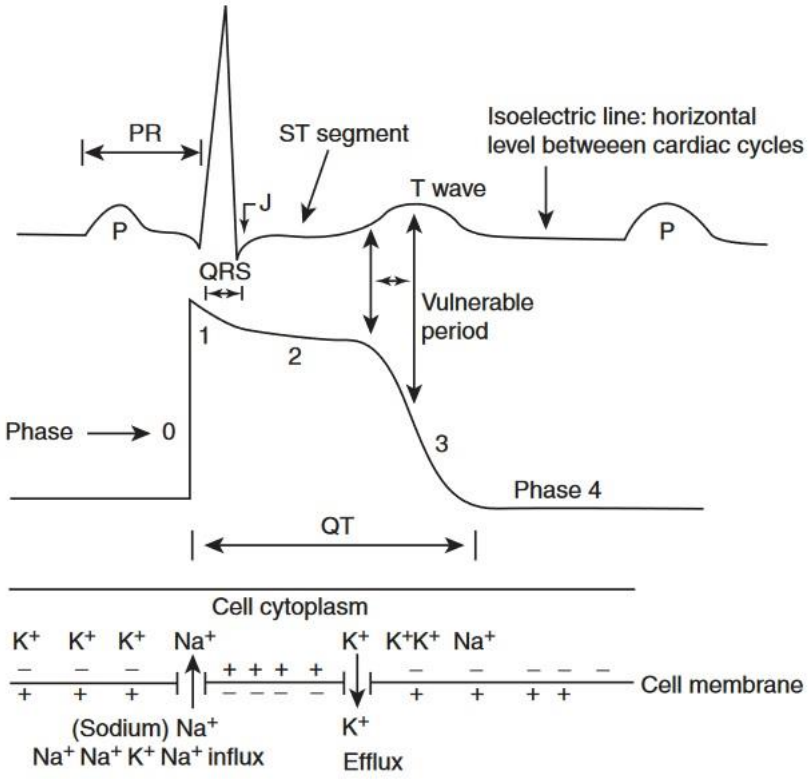

Figure 2. The electrocardiogram and the action potential (Khan 2006).

The QT interval varies with heart rate: with increased heart rate comes shorter QT interval (Tisdale 2016). To detect changes in ventricular repolarization, the QT interval is corrected to account for heart rate variations, this is known as the QTc interval. Formulae used for correcting the QT interval are discussed in 2.1.1.

The definition of a prolonged QT interval varies. Females have on average longer QT intervals than males, a difference appearing around puberty (Thomas and Behr 2015). This difference is recognized in some of the definitions of prolonged QT interval. American Heart Association uses the 99th percentiles of the population to define an abnormally prolonged QT interval (Drew et al. 2010). The QTc values are 470 ms for males and 480 ms for females. A QTc >500 ms is regarded as highly abnormal for both sexes. Another definition of a prolonged QT after heart rate correction with Bazett's correction formula is >450 ms for adult males and >470 ms for adult females (Goldenberg et al. 2006). In the guideline ICH E14, QT interval values of 450 ms, 480 ms and 500 ms are regarded as prolonged (European Medicines Agency 2005a). An increase in QTc of

>30 ms and certainly of >60 ms compared with the baseline value should be considered abnormal.

2.1.1 QT correction formulae

In the development of QT correction formulae, mainly resting ECGs have been used (Goldenberg et al. 2006). Due to this, when using correction formulae, a stable sinus rhythm without sudden changes in the RR interval is needed. Exponential, linear and logarithmic formulae have been developed. Table 1 shows different QT correction formulae. Bazett's correction formula is the most commonly used of these (Goldenberg et al. 2006).

Table 1. QT correction formulae (adapted from Goldenberg et al. 2006; Vandenberk et al. 2016)

Method	**Formula**
Exponential	
Bazett	$QTc = QT/RR^{1/2}$
Fridericia	$QTc = QT/RR^{1/3}$
Linear	
Framingham	$QTc = QT+0.154(1-RR)$
Hodges	$QTc = QT+0.00175\ ([60/RR]-60)$
Rautaharju	$QTc = QT-0.185\ (RR-1)+K$ (K = +0.006 seconds for men and +0 seconds for women)
Logarithmic	
Ashman	$QT = K1 \times \log(10 \times [RR + K2])$
Adult men	K1 = 0.380, K2 = 0.07
Adult women	K1 = 0.390, K2 = 0.07

RR = RR interval, QT = QT interval. QT and RR measured in seconds.

Bazett's correction formula has a problem with over and under correction of the QT interval, at both slow and fast heart rates it may give wrong results (Goldenberg et al. 2006; Vandenberk et al. 2016). Fridericia's correction formula is also widely used and performs better at faster heart rates. Framingham's and Rautaharju's correction formulae may perform better over a wide range of heart rates (Goldenberg et al. 2006). A study by Vandenberk et al. (2016) showed that Fridericia's and Framingham's correction formulae significantly improved prediction of 30-day and 1-year mortality of 6609 patients.

Correcting the QT interval at low heart rates with Ashman's correction formula gives values that are too low (Goldenberg et al. 2006).

2.2 Potential causes of QT interval prolongation and torsades de pointes

Both congenital and acquired long QT syndrome are caused by factors disturbing critical ion channels that are required for the proper heart function (Ackerman 2004). The common cause of both syndromes involves genetics and/or drugs or disease. The disturbances may result in QT prolongation due to abnormal cardiac repolarization. The symptoms of cLQTS are generally triggered by emotional or physical stress and patients are typically young people (Schwartz et al. 2012). QT prolongation may lead to polymorphic (i.e. the morphology of the QRS complexes is variable and not constant) ventricular tachycardia, TdP (Ackerman 2004; Tisdale 2016). In the ACC/AHA/ESC (American College of Cardiology/American Heart Association/European Society of Cardiology) 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, it is stated that TdP is "characterized by VT associated with a long QT or QTc, and electrocardiographically characterized by twisting of the peaks of the QRS complexes around the isoelectric line during the arrhythmia:

- 'Typical,' initiated following 'short-long-short' coupling intervals
- Short coupled variant initiated by normal-short coupling." (Zipes et al. 2006).

The symptoms of TdP are related to occurrence of rapid heart rate and the effects on blood pressure and cardiac output (Tisdale 2016). The symptoms include palpitations, dizziness, shortness of breath and syncope. There is no threshold for when TdP is certain to occur (Drew et al. 2010). Both studies on cLQTS and drug-induced long QT syndrome (diLQTS) have shown that a QTc >500 ms is associated with 2- to 3-fold higher risk of TdP compared to a QTc <500 ms. TdP may worsen and lead to VF and sudden cardiac death (Ackerman 2004; Schwartz and Woosley 2016). The heart rhythm may spontaneously recover or be defibrillated to normal sinus rhythm in time (Ackerman 2004).

The incidence of drug-induced TdP in the general population is largely unrecognized (Darpö 2001). The World Health Organization Drug Monitoring Centre received reports on 761 cases of TdP between 1983-1999. Of these, 32 cases were fatal. However, the reports only showed a suspicion of association between a drug and TdP, as various other factors may have influenced the reporting of a specific adverse event. A study investigating the public version of the US Food and Drug Administration Adverse Event Reporting System, found 1665 reports of TdP from 2004-2007, involving 376 active substances (Poluzzi et al. 2009). A Swedish study estimated an incidence of 4 cases of TdP per 100,000 persons annually (Darpö 2001). Another Swedish study, investigating TdP cases in the Swedish pharmacovigilance database, found 88 cases of TdP reported to the database during 1991-2006 (Åström-Lilja et al. 2008). In addition to pharmacotherapy, two or more risk factors for TdP was found in 85% of the cases. Heart disease (90% of the cases), age >65 years (72% of the cases) and female sex (70% of the cases) were the most common risk factors. The incidence of TdP after use of QT prolonging drugs may range from 2-12% depending on the drug, administered dose and the user's other risk factors (Tisdale 2016).

2.2.1 Congenital long QT syndrome

Congenital long QT syndrome (cLQTS) is a rare disease, researchers have found the prevalence to be anywhere from 1/5,000 to 1/20,000 (Schwartz et al. 2009). However, a study by Schwartz et al. (2009) found that the prevalence might be close to 1/2,000. Since the discovery of the inherited forms of LQTS in the 1950 and 1960s, it has been found that cLQTS is caused by mutations in ion channel genes or genes that code for proteins responsible for electrical activity in myocytes (Saenen and Vrints 2008). Sixteen genes have been associated with LQTS (Schwartz 2013). Alterations in ion currents, such as decreases in repolarizing outward potassium currents or increases in inward sodium or calcium currents, which are depolarizing, may lead to QT prolongation (Schwartz et al. 2012). Approximately 75% of all cases of cLQTS are associated with three genes; KCNQ1 (subtype LQT1), KCNH2 (subtype LQT2) and SCN5A (subtype LQT3) (Table 2) (Schwartz 2013). Heterozygous mutations in KCNQ1 cause the dominant Romano-Ward LQT1 syndrome, which is the most common of the disease-causing variants.

Another hereditary variant is Jervell and Lange-Nielsen syndrome which is caused by homozygous or compound heterozygous mutations in KCNQ1 and is associated with congenital deafness. Gene mutations can also appear as "silent mutations", that is, the mutations have no clinical expression (Morita et al. 2008; Schwartz et al. 2012). Of subtype LQT1 patients, 36% are silent mutation carriers (Schwartz et al. 2012). Of LQT2 patients and LQT3 patients, 19% and 10% are silent mutation carriers, respectively. In these patients, arrhythmias may be triggered by several risk factors. These risk factors will be discussed in 2.2.3.

Table 2. Overview of the long QT syndrome subtypes (Morita et al. 2008).

	LQT1	**LQT2**	**LQT3**
Associated genes	KCNQ1	KCNH2 (formerly known as hERG)	SCN5A
Affected ion current	I_{Ks}	I_{Kr}	I_{Na}
Triggers of arrhythmia	Emotional stress, exercise (swimming)	Emotional stress, exercise (acoustic, postpartum), rest	Emotional stress, rest, sleep
Occurrence	42-54%	35-45%	1.7-8%

Schwartz et al. (2012) presented a score for diagnosing LQTS, the "Schwartz score", in 1993. With a score of 3.5, patients have a high probability of LQTS. The score is useful for patients with suspected LQTS, for selecting patients who benefit from undergoing molecular screening (Schwartz score ≥3.0) and for identification of all affected family members.

2.2.2 Acquired long QT syndrome

Acquired long QT syndrome (aLQTS) is the more prevalent form of LQTS (van Noord et al. 2010). There are many risk factors for aLQTS (Schwartz and Woosley 2016; Vandael et al. 2017b). Demographic factors such as higher age and female sex, certain conditions and morbidities as well as electrolyte disturbances are known risk factors. Use of QT prolonging drugs is the most common cause of aLQTS (also known as diLQTS) (van Noord et al. 2010). It is suggested that persons with drug-induced TdP may carry mutations associated with LQTS, these persons have "a subclinical form of the congenital

syndrome" (Roden 2004). Polymorphisms may modulate patients' susceptibility to QT prolongation and TdP. QT prolonging drugs, gene-drug interactions and DDIs will be discussed in Chapter 3. To explain the variable risk of QT prolongation in patients, the term "repolarization reserve" was introduced by Roden in 1998, explaining physiological mechanisms that maintain normal cardiac repolarization (Roden 1998; Roden 2004). The mechanisms protect against risk factors that may disturb normal ventricular repolarization. More available risk factors make a person more susceptible to QT prolongation and TdP, thus having a reduced reserve.

2.2.3 Non-pharmacological risk factors associated with QT interval prolongation and torsades de pointes

There are many studies and reviews discussing the risk factors for QT prolongation. However, few have gathered and assessed the evidence for various risk factors. The systematic review by Vandael et al. (2017b) summarized and assessed risk factors for QT prolongation such as demographic factors, comorbidities, electrolyte disturbances and QT prolonging drugs from ten observational studies. Several of the risk factors in this systematic review can be found on the list of risk factors for QT prolongation and/or TdP (Table 3) that Arizona Center for Education and Research (AZCERT) maintains (Woosley et al. 2018c) The risk factors have been placed on the list based on a systematic review and analysis of available evidence. The quality of the evidence and the strength of associations were assessed using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale (Balshem et al. 2011).

Risk for TdP increases in patients with multiple clinically recognizable risk factors (Drew et al. 2010). In a study with cases of TdP, most patients had at least one identified risk factor (Zeltser et al. 2003). Of the cases, 71% had two risk factors or more. In a study from 2015 in patients with severely prolonged QT interval, QT prolonging drugs were responsible for 48% of the cases of QT prolongation (Laksman et al. 2015).

Table 3. Risk factors for QT prolongation and/or TdP (Woosley et al. 2018c).

	Clinical risk factors	Clinical association with increased QT interval	Quality of evidence for association with increased QT interval	Clinical association with TdP	Quality of evidence for association with TdP
Autonomic nervous system	Pheochromocytoma	Yes	High	Yes	High
	Alpha adrenergic stimulation	Yes	Moderate	Yes	Low
	Emotion (arousal)	Yes	Moderate	Yes	Moderate
	Cold water immersion	Yes	Moderate	Yes	Moderate
Cardio-vascular diseases	Bradycardia, AV block, pause	Yes	High	Yes	High
	Takosubo (stress-related) cardiomyopathy	Yes	High	Yes	High
	Acute myocardial ischemia	Yes	Moderate	Yes	Low
	Stroke	Yes	High	Yes	Low
	Hypertension/LVH[1]	Yes	Low	Weak	Very low
	Mitral valve prolapse	Yes	Moderate	Weak	Very low
	Cardiomyopathy/CHF[2]	Yes	Moderate	Weak	Low
	Atrial fibrillation conversion	Weak	Moderate	Yes	Moderate
	Hypertrophic cardiomyopathy	Weak	Low	Weak	Low
Electrolyte disorders	Hypokalemia (≤3.5 mEq/L)	Yes	High	Yes	High
	Hypomagnesemia (≤1.7 mg/dL)	Yes	High	Yes	High
	Hypocalcemia (≤8.5 mg/dL)	Yes	High	Yes	Moderate
	Hyperemesis (anorexia nervosa, pregnancy)	Yes	Moderate	Weak	Low
	Diarrhea	Yes	Moderate	Weak	Very low
	Excessive ingestion of licorice	Yes	High	Yes	Moderate
	Bartter syndrome	Yes	Moderate	Weak	Very low
	Hemodialysis	Yes	Moderate	Weak	Very low

	Hypernatremia (extreme)	Yes	Low	Yes	Very low
Endocrine disorders	Hypothyroidism	Yes	High	Yes	Moderate
	Hyperthyroidism	Yes	Low	Weak	Very low
	Hypoglycemia	Yes	Moderate	Yes	Moderate
	Hyperglycemia	Yes	Low	Weak	Very low
	Diabetes	Weak	Low	Weak	Very low
	Primary aldosteronism	Yes	Moderate	Yes	Moderate
	Panhypopituitarism	Yes	Moderate	Yes	High
	Hyperparathyroidism	Yes	High	Weak	Very low
General clinical factors	Female sex	Yes	High	Yes	High
	Age ≥65 years	Yes	High	Yes	Low
	Renal failure (GFR ≤30 ml/min)	Yes	Low	Yes	Very low
Inflammation/ Auto-immune factors	Sepsis	Yes	Moderate	Yes	Moderate
	Cytokines (TNFα, IL1β, IL6)	Yes	Moderate	Weak	Low
	Fever	Yes	Moderate	Yes	Low
	Inflammation/ Rheumatoid arthritis	Yes	Moderate	Yes	Moderate
	Sarcoidosis	Yes	Low	Weak	Very low
	Anti SSA/Ro antibody	Yes	Low	Weak	Very low
Environ-mental effects	Hypothermia	Yes	High	Yes	Moderate
	Herbal remedies	Weak	Low	Weak	Very low
	Chlorobutanol	Yes	Low	Yes	Low
Miscellaneous	Genotypic association	Yes	High	Yes	High
	Ferritin/Iron overload	Yes	Moderate	Weak	Low
	Liquid protein diet	Yes	High	Yes	Moderate
	Sickle cell disease	Yes	High	Weak	Very low
	Congenital generalized lipodystrophy (PTRF)	Yes	Moderate	Weak	Very low
	[1] Left ventricular hypertrophy [2] Congestive heart failure				

3 DRUGS ASSOCIATED WITH QT PROLONGATION AND TORSADES DE POINTES

According to the QTDrugs Lists of CredibleMeds maintained by AZCERT, about 200 drugs have the potential to prolong the QT interval and/or cause TdP (Woosley et al. 2018b). The drugs associated with QT prolongation and TdP belong to different drug classes. Most of the drugs associated with QT prolongation act by inhibiting the rapid component of the delayed rectifier potassium channel (I_{Kr}), i.e. delaying cardiac repolarization (van Noord et al. 2010; Thomas and Behr 2016). I_{Kr} is encoded by the KCNH2 gene (formerly known as hERG). The inhibition of I_{Kr} is not specific (van Noord et al. 2010) Some drugs associated with QT prolongation lack the torsadogenic effect. Cardiac arrhythmia may also manifest itself without QT prolongation. A few drugs are known to inhibit I_{Na} (sodium channel). I_{Na} inhibiting drugs may cause delayed intraventricular conduction which may result in VT or VF. Examples of drugs inhibiting I_{Na} are certain antihistamines, β blockers, phenothiazines and tricyclic antidepressants.

QT prolongation and association with TdP have been one of the most common reasons for withdrawal or restriction of the use of marketed drugs in the past two decades (Roden 2004; Pelkonen and Pasanen 2006; Nurminen 2015). Nonclinical and clinical studies are recommended for assessing risk of QT prolongation and cardiovascular adverse events when developing new drugs. ICH published guidelines in 2005, ICH E14 (clinical studies) and ICH S7B (preclinical testing) (European Medicines Agency 2005a; European Medicines Agency 2005b). A safety pharmacology study, a “thorough QT/QTc study (TQT study)” is carried out in early clinical development and conducted in healthy volunteers. Further safety evaluations in later development phases are needed if the drug seem to be associated with TdP in the TQT study. A benefit-risk ratio analysis should be conducted and possible risk management after approval of the drugs should be stated. Post-marketing surveillance is important and post-marketing surveillance has helped to identify rare adverse events of drugs, such as TdP, after the drugs are available on the market (Roden 2004).

3.1 Drugs on the QTDrugs Lists of CredibleMeds

Due to the growing concern for drug-induced TdP, Georgetown University Center for Education and Research on Therapeutics, USA was awarded a federal grant in 1999 (Schwartz and Woosley 2016). The aim was to assess drugs with risk of causing TdP with available evidence and to provide the findings freely available to the medical community and the public. The center was later moved to University of Arizona and became in 2012 a freestanding nonprofit organization, AZCERT. AZCERT maintains the CredibleMeds website and a Scientific Review Committee, including three physician members, conducts ongoing research on drugs associated with QT prolongation and TdP and assess the evidence with the Bradford-Hill criteria (Woosley et al. 2018a). Drugs are regularly monitored for new evidence and the QTDrugs Lists are updated every four to eight weeks (Schwartz and Woosley 2016). The decisions and recommendations made by the Scientific Review Committee is reviewed by an International Advisory Board of 39 authorities on drug safety and cardiovascular medicine (Woosley et al. 2018a).

Drugs are categorized into four TdP risk categories (Woosley et al. 2018a,b). QTDrugs List 1 contains drugs that prolong the QT interval and are known for their risk of TdP, even when taken as recommended (Table 4). QTDrugs List 2 contains drugs that can cause QT prolongation but there is a lack of evidence of TdP risk when taken as recommended (Table 5). QTDrugs List 3 contains drugs that under certain circumstances are associated with TdP (Table 6). These circumstances may be hypokalemia, excessive dose or if the drugs are taken with interacting drugs. TdP can also be induced by for example inhibiting the metabolism of the QT prolonging drug or by electrolyte disturbances. QTDrugs List 4 contains drugs from the above-mentioned categories that pose risk for people with cLQTS as well as certain drugs that do not prolong the QT interval as such but have a special risk because their other actions. A Swedish study identifying TdP cases in the Swedish pharmacovigilance database, found that TdP or QT prolongation was labelled in the summary of product characteristics for 33% (n=9/27) of the drugs implicated in the 88 TdP cases identified (Åström-Lilja et al. 2008). The QTDrugs Lists of CredibleMeds may therefore function as a useful tool for health care professionals seeking information on QT prolonging drugs.

Table 4. Drugs on the Finnish market with known risk of TdP (QTDrugs List 1) in 2017 (Finnish Medicines Agency 2017; Woosley et al. 2018b).

Generic Name	Drug Class	Therapeutic Use
Amiodarone	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Phosphodiesterase-3 inhibitor	Thrombocythemia
Arsenic trioxide	Anticancer	Cancer (leukemia)
Azithromycin	Antibiotic	Bacterial infection
Ciprofloxacin	Antibiotic	Bacterial infection
Citalopram	Antidepressant, SSRI	Depression
Clarithromycin	Antibiotic	Bacterial infections
Donepezil	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Antipsychotic/Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	Antibiotic	Bacterial infection, increase gastrointestinal motility
Escitalopram	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Antifungal	Fungal infection
Haloperidol	Antipsychotic	Schizophrenia, agitation
Ibutilide	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Antibiotic	Bacterial infection
Levomepromazine	Antipsychotic	Schizophrenia
Methadone	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Antibiotic	Bacterial infection
Ondansetron	Antiemetic	Nausea, vomiting
Oxaliplatin	Antineoplastic agent	Cancer
Propofol	Anesthetic, general	Anesthesia
Roxithromycin	Antibiotic	Bacterial infection
Sevoflurane	Anesthetic, general	Anesthesia
Sotalol	Antiarrhythmic	Abnormal heart rhythm
Terlipressin	Vasoconstrictor	Septic shock
Vandetanib	Anticancer	Cancer (thyroid)

Table 5. Drugs with possible risk of TdP (QTDrugs List 2) on the Finnish market in 2017 (Finnish Medicines Agency 2017; Woosley et al. 2018b).

Generic Name	Drug Class	Therapeutic Use
Alfuzosin	Alpha1-blocker	Benign prostatic hyperplasia
Apomorphine	Dopamine agonist	Parkinson's disease
Aripiprazole	Antipsychotic, atypical	Schizophrenia, depression (adjunct)
Asenapine	Antipsychotic, atypical	Schizophrenia
Atomoxetine	Norepinephrine reuptake inhibitor	ADHD

Bedaquiline	Antibiotic	Tuberculosis, Multi-drug resistant
Bendamustine	Alkylating agent	Leukemia, lymphoma
Bortezomib	Proteasome inhibitor	Cancer (multiple myeloma, lymphoma)
Bosutinib	Tyrosine kinase inhibitor	Cancer (leukemia)
Buprenorphine	Opioid receptor modulator	Narcotic addiction and pain
Cabozantinib	Anti-cancer	Renal cell carcinoma
Capecitabine	Anticancer	Cancer (GI, Breast)
Ceritinib	Kinase inhibitor	Cancer (Lung)
Clomipramine	Antidepressant, Tricyclic	Depression
Clozapine	Antipsychotic, atypical	Schizophrenia
Crizotinib	Kinase inhibitor	Cancer (Non-small cell lung cancer, metastatic)
Dabrafenib	Kinase inhibitor	Cancer (melanoma)
Dasatinib	Tyrosine kinase inhibitor	Cancer (leukemia)
Degarelix	Gonadotropin Releasing Hormone Agonist/antagonist	Cancer (prostate)
Dexmedetomidine	Sedative	Sedation
Efavirenz	Antiretroviral	HIV
Eliglustat	Glucosylceramide synthase inhibitor	Gaucher's disease
Epirubicin	Anti-cancer	Cancer
Eribulin mesylate	Microtubule inhibitor	Cancer (breast, metastatic)
Ezogabine (Retigabine)	Anticonvulsant	Seizures, partial
Fingolimod	Sphingosine phospate receptor modulator	Multiple Sclerosis
Fluorouracil	Anti-cancer	Cancer
Flupentixol	Dopamine 2 and 5HT2a antagonist	Schizophrenia
Granisetron	Antiemetic	Nausea, vomiting
Isradipine	Antihypertensive	Hypertension
Lapatinib	Kinase inhibitor	Cancer (breast, metastatic)
Lenvatinib	Anticancer	Cancer (Thyroid)
Lithium	Antimania	Bipolar disorder
Lopinavir/ritonavir	Viral protease inhibitor	HIV/AIDS
Mifepristone	Progesterone antagonist	Pregnancy termination
Mirabegron	Beta-3 adrenergic antagonist	Bladder spasm
Mirtazapine	Antidepressant, Tetracyclic	Depression
Necitumumab	Anti-cancer	Lung Cancer
Nilotinib	Kinase inhibitor	Cancer (leukemia)
Nortriptyline	Antidepressant, Tricyclic	Depression
Nusinersen	Antisense oligonucleotide	Spinal Muscular Atrophy
Ofloxacin	Antibiotic	Bacterial infection
Osimertinib	Tyrosine kinase inhibitor	Cancer (EGFR pos. NSC Lung cancer)
Oxytocin	Oxytocic	Labor stimulation
Paliperidone	Antipsychotic, atypical	Schizophrenia

Palonosetron	Antiemetic	Nausea
Pasireotide	Somatostatin analog	Cushing's Disease
Pazopanib	Tyrosine kinase inhibitor	Cancer (renal cell, sarcoma)
Perflutren lipid microspheres	Imaging contrast agent	Echocardiography
Perphenazine	Antipsychotic	Schizophrenia
Rilpivirine	Antiviral	Viral infection (HIV/AIDS)
Risperidone	Antipsychotic, atypical	Schizophrenia
Saquinavir	Antiviral	Viral infection (HIV/AIDS)
Sertindole	Antipsychotic, atypical	Schizophrenia, anxiety
Sorafenib	Tyrosine kinase inhibitor	Cancer (liver, renal cell, metastatic thyroid)
Sunitinib	Kinase inhibitor	Cancer (GIST, renal cell, pNET)
Tacrolimus	Immunosuppressant	Immune suppression
Tamoxifen	Anticancer	Cancer (breast)
Tetrabenazine	Vesicular Monoamine Transporter 2 Inhibitor	Chorea (Huntington's disease)
Tizanidine	Muscle relaxant	Muscle spasticity
Tolterodine	Muscle relaxant	Bladder spasm
Toremifene	Estrogen agonist/antagonist	Cancer (breast, metastatic)
Tramadol	Analgesic	Pain
Trimipramine	Antidepressant, Tricyclic	Depression
Vardenafil	Phosphodiesterase 5 inhibitor	Erectile dysfunction
Vemurafenib	Kinase inhibitor	Cancer (melanoma)
Venlafaxine	Antidepressant, SNRI	Depression
Inotuzumab ozogamicin	Antibody-drug conjugate	Leukemia

Table 6. QTDrugs List 3: Conditional risk of TdP, drugs available on the Finnish market in 2017 (Finnish Medicines Agency 2017; Woosley et al. 2018b).

Generic Name	Drug Class	Therapeutic Use
Amitriptyline	Antidepressant, Tricyclic	Depression
Amphotericin B	Antifungal	Fungal infection
Atazanavir	Antiviral	Viral infection (HIV/AIDS)
Diphenhydramine	Antihistamine	Allergic rhinitis, insomnia
Doxepin	Antidepressant, Tricyclic	Depression
Esomeprazole	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Fluoxetine	Antidepressant, SSRI	Depression
Fluvoxamine	Selective Serotonin Reuptake Inhibitor	Depression, Obsessive Compulsive Disorder
Furosemide (frusemide)	Diuretic	Hypertension, diuresis
Galantamine	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Hydrochlorothiazide	Diuretic	Hypertension, diuresis
Hydroxychloroquine	Antimalarial, Anti-inflammatory	Malaria, SLE, rheumatoid arthritis

Hydroxyzine	Antihistamine	Allergic reaction, anxiety disorders
Indapamide	Diuretic	Hypertension, diuresis
Itraconazole	Antifungal	Fungal infection
Ivabradine	Antianginal	Angina Pectoris (heart pain)
Ketoconazole	Antifungal	Fungal infection
Lansoprazole	Proton Pump Inhibitor	Proton-pump inhibitor
Loperamide	Opiate	Diarrhea
Metoclopramide	Antiemetic	Nausea, vomiting
Metronidazole	Antibiotic	Trichomoniasis, amebiasis, bacterial infection
Olanzapine	Antipsychotic, atypical	Schizophrenia, bipolar disorder
Omeprazole	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Pantoprazole	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Paroxetine	Antidepressant, SSRI	Depression
Piperacillin/Tazobactam	Antibacterial	Bacterial infection
Posaconazole	Antifungal	Fungal infection
Quetiapine	Antipsychotic, atypical	Schizophrenia
Sertraline	Antidepressant, SSRI	Depression
Solifenacin	Muscle relaxant	Bladder spasm
Trazodone	Antidepressant, SARI	Depression, insomnia
Voriconazole	Antifungal	Fungal infection
Ziprasidone	Antipsychotic, atypical	Schizophrenia
Famotidine	H_2-receptor antagonist	Gastric hyperacidity, GERD

3.2 Drug-drug interactions contributing to QT prolongation

Pharmacodynamic DDIs may lead to QT prolongation if the individual QT prolonging drugs have an additive or potentiating effect (Aerssens and Paulussen 2005). Pharmacokinetic DDIs may also cause QT prolongation. A drug may reduce the clearance of a concomitantly used QT prolonging drug. This leads to increased plasma and tissue concentrations. Pharmacokinetic DDIs may involve drugs metabolized by cytochrome P450 enzymes (CYP enzymes) and may lead to increased plasma concentrations. Many drugs associated with diLQTS are metabolized by CYP3A and CYP2D6.

QT prolonging DDIs increase the risk of TdP (INXBASE 2018). In a study in 249 patients with drug-induced TdP, potential interactions with QT prolonging drugs were found in 39% of the patients (Zeltser et al. 2003). Antihistamines−macrolides or imidazole antibiotics; concomitant use of QT prolonging antipsychotics; cisapride−erythromycin as

well as antibiotics (macrolides or quinolones)−antiarrhythmic drugs stood for most of the DDIs. In 35% of the patients, potential interference with the metabolism of a QT prolonging drug by another drug was present. Pharmacokinetic interactions were seen with cisapride, nifedipine, propranolol and diazepam. Erythromycin with antihistamines or cisapride were also recognized pharmacokinetic interactions.

3.3 Gene-drug interactions

Ion-channel mutations increasing the risk of QT prolongation by drug use, genetic variants potentiating a drug's QT prolonging effect and polymorphism in drug metabolism influencing the pharmacokinetics of drugs are examples of gene-drug interactions (van Noord et al. 2010). Mutations in cLQTS genes may be asymptomatic but after exposure to QT prolonging drugs, the patient is more susceptible to inhibition of KCNH2-encoded potassium channels and QT prolongation may occur. A Finnish research group conducted a study to clarify the assumed role of subclinical inherited LQTS in drug-induced TdP in 16 Finnish patients (Lehtonen et al. 2007). Four potassium channel mutations were associated with over 70% of the mutations causing cLQTS in Finland. In 19% of the patients LQTS-causing mutations could be identified. The frequency was higher than in previous studies, in about 5% of drug-induced TdP cases previously disguised, LQTS was identified.

Increased susceptibility for aLQTS may be caused by polymorphism in cLQTS genes (Aerssens and Paulussen 2005). Various polymorphic nucleotides have been identified, confirmed to have consequences in the cLQTS genes. Allele frequencies may vary in different ethnicities. NSO1AP gene polymorphism has been found to potentiate the QT prolonging effect of verapamil (van Noord et al. 2010). Polymorphism in drug metabolizing enzyme genes are also important. Of the Caucasian population, approximately 5-10% are "poor metabolizers" of CYP2D6 and have an increased risk of developing QT prolongation or TdP when using QT prolonging drugs metabolized by this CYP enzyme. Polymorphism in drug transporter genes are also possible. This can lead to changes in drug clearance or drug concentrations which may impact the QT interval.

4 PREVENTION AND MANAGEMENT OF DRUG-INDUCED QT PROLONGATION AND TORSADES DE POINTES

There are several guidelines available describing management of the risk of QT prolongation and TdP in hospital settings and psychiatry (Ames et al. 2002; Royal College of Psychiatrists London 2006; Drew et al. 2010, Fanoe et al. 2014). Guidelines recommend that attention should be given especially to patients with higher risk (Royal College of Psychiatrists London 2006; Drew et al. 2010). The guideline by Ames et al. (2002) describes a team approach to the management of patients with schizophrenia, considering both various medical practitioners and pharmacists. Several antipsychotic drugs have the potential to cause QT prolongation and TdP (Woosley et al. 2018b). Despite the existing guidelines, the adherence to them is considered low (Tay et al. 2014; Vandael et al. 2016). This might be due to limited awareness and knowledge of the risks of QT prolongation and TdP, lack of feasibility of the guidelines or the lack of guidelines for a specific area, such as primary care and community pharmacies (Fongemie et al. 2013; Choo et al. 2014; Vandael et al. 2018). In a study by Viskin et al. (2005), more than 60% of non-cardiologists could not accurately calculate a QT interval and could not correctly identify QT prolongation in patients.

There is potential for pharmacists to play a key role in the management of the risk of QT prolongation, as they may be able to detect DDIs with risk of QT prolongation (Vandael et al. 2018). However, in a survey by Vandael (2016) it was revealed that the knowledge of QT prolongation in pharmacists and pharmacy students was limited. An e-learning program about the risk and management of QT prolongation, including tools for clinical practice, such as risk scores, was developed by Vandael et al. (2018) and was implemented in a Flemish pharmacy network. The pharmacists participating in the study were satisfied with the training and the e-learning resulted in increased knowledge of QT prolongation. Similar education was held in Indiana University Health Methodist Hospital (Tisdale et al. 2014). Tisdale et al. (2014) developed a clinical decision support system (CDSS) for reducing the risk of QT prolongation in cardiac care units. Before activation of the CDSS, pharmacists and physicians were educated on QT prolongation and TdP. They were also educated on the CDSS, the incorporated risk score for assessing

patients' risk of QT prolongation as well as the role of health care providers in the CDSS alert process.

4.1 Prescribing of QT prolonging drugs

When contemplating pharmacotherapy with a QT prolonging drug, patient-specific risk factors (Chapter 2.2.3) need to be considered (Roden 2004; Drew et al. 2010). The risk-benefit ratio needs to be assessed individually and where efficacy of alternative pharmacotherapy is equivalent, the non-QT prolonging drug should be prescribed (Drew et al. 2010). QT prolongation should not limit the pharmacotherapy in cases where benefit clearly outweighs risk. For the majority of QT prolonging drugs, risk increases as a function of dose and plasma drug concentration. The route of administration should also be considered. Higher drug concentrations and greater cardiac exposure may be attained by intravenous administration as opposed to oral administration, thus creating risk for TdP. It also appears that rapid infusions of higher drug doses are more likely to cause TdP than slower infusions. The lowest effective dose of a QT prolonging drug should therefore be used and when the pharmacotherapy is no longer required, discontinued (Thomas and Behr 2015). Methods for reducing the risk of QT prolongation and TdP can be found in Table 7. Patients should be informed to report any symptoms such as new palpitations, near-syncope or syncope when starting QT prolonging pharmacotherapy (Roden 2004). Intercurrent conditions and concomitantly used therapies that may cause electrolyte imbalance should also be reported to a health care professional.

Table 7. Methods for reducing the risk of QT prolongation and TdP (Drew et al. 2010; Tisdale 2016).

• Avoid use of QT prolonging drugs in patients known to have baseline QTc intervals >450 ms
• In cases where the QTc interval prolongs to >500 ms, discontinue QT prolonging drug(s)
• In cases where the QTc interval increases ≥60 ms from baseline value, reduce the dose or discontinue QT prolonging drug(s)
• Maintain serum electrolyte concentrations within normal range
• Avoid the use of QT prolonging drugs in patients with heart failure and a left ventricular ejection fraction <20%
• Avoid clinically significant drug-drug interactions
• In patients with acute kidney injury or chronic kidney disease, adjust doses of renally eliminated QT prolonging drugs
• Rapid administration of intravenous QT prolonging drugs needs to be avoided
• Avoid concomitant use of QT prolonging drugs
• Avoid use of QT prolonging drugs in patients with a history of drug-induced TdP or in those who have previously been resuscitated from an episode of sudden cardiac death
• Avoid use of QT prolonging drugs in patients who have been diagnosed with cLQTS

4.2. Monitoring of the QT interval

AHA recommend that QT interval monitoring in hospital settings is indicated at initiation of a drug known to cause TdP, overdose on potentially proarrhythmic agents, new-onset bradyarrhythmias and severe electrolyte imbalances, such as hypokalemia or hypomagnesemia (Drew et al. 2010). An electrolyte panel blood test before prescribing QT prolonging drugs and during care with QT prolonging drugs may be necessary (Thomas and Behr 2015). Baseline ECGs and QT interval monitoring at least every 8 to 12 hours after initiation of QT prolonging drugs may be necessary (Drew et al. 2010). Increased dose or overdose of QT prolonging drugs also requires QT interval monitoring. More frequent monitoring is indicated if QT prolongation is observed. The duration of the QT interval monitoring depends on the drug's half-life, elimination of the drug or whether the drug is given regularly or as needed. Additionally, it depends on how long it takes for the QTc to return to the baseline value and whether the monitoring shows arrhythmias. Patients receiving pharmacotherapy with a drug with a high risk of torsadogenic effect may require continuous QTc monitoring in a hospital setting. A defibrillator should also be available.

There are several methods for monitoring the QT interval in an inpatient setting, but the best method is still unknown (Drew et al. 2010). Standard 12-lead ECGs may be

performed, and a heart rate corrected QT interval calculated. Where continuous ECG monitoring has been performed, manual measurement of the QT interval with handheld calipers using rhythm strips from cardiac monitors have been used. The QT interval has been corrected traditionally with Bazett's correction formula, although it may under correct or over correct the QT interval (Drew et al. 2010; Vandenberk et al. 2016). There are also fully automated monitoring systems where the QTc interval is monitored in real-time (Drew et al. 2010).

ECG monitoring for QT prolongation and TdP is manageable in a hospital setting. Recommendations concerning the relevant frequency of ECG monitoring for determination of the QT interval in outpatients receiving QT prolonging pharmacotherapy however, have not been widely declared (Tisdale 2016). QTc is an indicator of TdP risk but it does not fully account for all risk by itself (Malik 2001; Roden 2004; Drew et al. 2010). As TdP is dependent on the presences of patients' underlying risk factors, identifying adjustable risk factors, such as electrolyte disturbances and QT prolonging drugs, may be more relevant than baseline ECG monitoring (Muzyk et al. 2012; Tisdale et al. 2013). Identifying patients with a considerable risk of QT prolongation and TdP and developing risk assessment tools, such as risk scores, can be easier and may be a more cost-effective way to reduce the risk (Tisdale et al. 2013). Risk assessment tools may identify patients with a higher risk of QT prolongation or TdP for whom repetitive or continuous ECG monitoring, discontinuation of QT prolonging drugs or monitoring of serum electrolyte concentration may be necessary (Tisdale et al. 2013; Vandael et al. 2017a). These methods may be used in inpatient settings as well as in outpatient settings and be used by different health care professionals, although mainly by prescribers and pharmacists (Tisdale 2016).

4.3 Management of QT prolongation and torsades de pointes

ACC/AHA/ESC 2006 guidelines recommend withdrawal of the QT prolonging pharmacotherapy and correction of electrolyte disturbances in patients with TdP and diLQTS (Zipes et al. 2006). Direct-current (electrical) cardioversion should be performed in patients with TdP that does not terminate spontaneously or in patients with TdP

degenerating into VF (Drew et al. 2010). It is reasonable to administer intravenous magnesium sulfate 2 g in patients with LQTS and few TdP episodes, although the mechanism for benefit is unknown (Zipes et al. 2006; Drew et al. 2010). Repeated doses may be needed. Repletion of potassium to levels of 4.5-5 mmol/l (supratherapeutic levels) may be considered. According to the guideline, reasonable treatment in patients with QT prolonging pharmacotherapy with recurrent TdP includes atrial and ventricular pacing or administration of isoproterenol, a non-selective β_1/β_2 agonist (Drew et al. 2010; Thomas and Behr 2015). Isoproterenol (isoprenaline) is a special permit product in Finland (Finnish Medicines Agency 2018). Beta blockade and pacing is a reasonable acute treatment for patients with TdP and sinus bradycardia.

5 RISK ASSESSMENT TOOLS

5.1 INXBASE

The DDI database SFINX (Swedish-Finnish Interaction X-referencing) was developed by a group of clinical pharmacologists, pharmacists, physicians and software developers from Finland (Turku University Hospital) and Sweden (Karolinska Institutet, Department of Drug Management and Informatics at the Stockholm County Council) (Böttiger et al. 2009) The interaction database was first released in Finland in 2005. The interaction database available in Finland nowadays is INXBASE developed by Medbase Ltd (Medbase 2018). INXBASE includes over 20.000 interactions and is updated quarterly. INXBASE uses the QTDrugs Lists of CredibleMeds as one reference for QT prolonging drugs (INXBASE 2018). The database is available for integration into CDSSs (Böttiger et al. 2009). Prescribers then receive alerts on DDIs automatically when prescribing. The majority of pharmacists in Finland have the interaction database available for use through electronic prescription delivery systems in pharmacies.

The DDI database is structured according to individual substance names, drug formulation and substance properties (Böttiger et al. 2009). The interactions are classified considering clinical relevance and level of documentation (Table 8). Clinical

recommendations are classified into four categories in accordance to the GRADE system, and the categories are color coded (Guyatt et al. 2008; Medbase 2018).

Table 8. Classification categories (with their respective color code) in INXBASE for clinical relevance and level of documentation (Böttiger et al. 2009; INXBASE 2018).

Classification	Definition
Clinical relevance	
A	Interaction of no clinical relevance
B	The clinical outcome of the interaction is unclear and/or may vary
C	Clinically relevant interaction. May be managed by e.g. dose adjustment
D	Clinically significant interaction, which is best avoided
Level of documentation	
0	Data derived from extrapolation based on studies with similar drugs
1	Data derived from incomplete case reports and/or in vitro studies
2	Data derived from well-documented case reports
3	Data derived from studies in healthy volunteers and/or pilot studies in patients
4	Data derived from controlled studies. Studies conducted in relevant patient populations

5.2 RISKBASE

The same working group that developed INXBASE (SFINX), developed PHARAO (Pharmacological Risk Assessment Online), a CDSS for creating a risk profile for adverse events, associated with the effects of concomitant drug use, including a risk profile for QT prolongation (Böttiger et al. 2017). Pharmacological handbooks, summaries of product characteristics, evaluations from European Medicines Agency, and articles found trough PubMed were searched for evaluation and scoring of 1427 substances. Nine pharmacological properties were chosen, with focus on adverse events relevant in older adults; risk of bleeding, sedation, orthostatism, constipation, anticholinergic and serotonergic adverse events, nephrotoxicity, seizures and the most important one due to the objective of this master's thesis, QT prolongation/arrhythmia. PHARAO, now called RISKBASE in Finland, was developed with the aim of complementing the DDI database INXBASE. About 1500 drugs regarding 11 clinically relevant adverse effects are

included in the updated version of RISKBASE (RISKBASE 2018). The latest addition enables analysis of patients' pharmacotherapy in terms of potassium and sodium balance, which may also provide aid in the assessment of risk of QT prolongation. Drug substances are scored from 0 (no pharmacological effect) to 3 (strong pharmacological effect) for all properties except nephrotoxicity and potassium and sodium balance (Böttiger et al. 2017; Medbase 2018; RISKBASE 2018). For renal toxicity, there is a score of 0 or 1 and for potassium and sodium balance -3 (decreasing effect) to +3 (increasing effect). Algorithms for each adverse event score are developed to create individual risk profiles. The risk level is divided into four categories based on clinical significance (Table 9). A severity-specific phrase for consequence and recommendation is given for each adverse event.

Table 9. Risk levels, with their respective color codes in RISKBASE (RISKBASE 2018).

Classification	Definition
A	No increased risk is known
B	Slightly increased risk
C	Moderately increased risk
D	Significantly increased risk

5.3 Risk scores

Several risk scores for QT prolongation has been developed in retrospective and prospective observational studies. All studies in which risk scores were applied, found evidence of QT prolonging drugs from the QTDrugs Lists of CredibleMeds (Haugaa et al. 2013; Tisdale et al. 2013; Vandael et al. 2016; Vandael et al. 2017a). Haugaa et al. from Mayo Clinic (2013) developed an institution-wide QT alert system including a pro-QTc risk score for assessment of mortality. In addition to QT prolonging drugs, the risk score included other risk factors for QT prolongation such as demographic factors, QT interval affecting clinical conditions and morbidities and electrolyte disturbances. The pro-QTc score was created from the sum of QT prolonging factors. A risk score of ≥4 indicated higher mortality. The limitation of the pro-QTc score was the lack of information on predictive performance and that each risk factor was considered equal and was allocated 1 point, owing to lack of specific data for each point.

Tisdale et al. (2013) developed a risk score in cardiac critical care units. This risk score did not include as many risk factors for QT prolongation as the pro-QTc score, but the risk score allocated weighted points based on log odds ratios for each risk factor. Based on total points, patients were placed into a low-risk (<7 points/21 points), moderate risk (7-10 points/21 points) or high-risk category (≥11 points/21 points). The study by Tisdale et al. (2013) showed that the risk score had good predictive performance. This risk score was later incorporated into a CDSS which alerted hospital pharmacists entering orders for QT prolonging drugs, who then could discuss risk mitigation strategies with the prescriber (Tisdale et al. 2014).

Vandael et al. (2016) developed a risk score based on the pro-QTc score by Haugaa et al. (2013), but later also developed the preliminary RISQ-PATH score in various hospital wards in University Hospitals Leuven (Vandael et al. 2017a). This risk score contained a high number of risk factors, obtained from a previously conducted systematic review of observational studies (Vandael et al. 2017b). Points in the risk score were allocated according to the evidence level of the risk factors from this systematic review. Drugs found on the QTDrugs Lists of CredibleMeds (lists 1-3) were allocated different points. A cut-off value of 10 points out of a total of 40.5 points + the sum of QT prolonging drugs was set as high-risk for QT prolongation. The preliminary RISQ-PATH score had good predictive performance. Based on an optimized RISQ-PATH model, an algorithm for a CDSS was proposed (Vandael 2016). This CDSS could create smart QT alerts based on ECG parameters and patient-specific risk factors.

6 QT PROLONGING PHARMACOTHERAPY IN OLDER ADULTS

QTc increases with age, especially in those over the age of 75, and a risk factor for QT prolongation age ≥65 years (Esen et al 2004; Rabkin 2015; Woosley et al. 2018c). The prevalence of risk factors, such as multiple illnesses, electrolyte disturbances and polypharmacy, increase in older adults, thus increasing their risk of QT prolongation and TdP (Drew et al. 2010; Moreno-Gutiérrez et al. 2016). The need for treatment of illnesses may increase with age (Rabkin 2015). For example, the treatment of cardiovascular

illness may include diuretics, which may in turn induce electrolyte disturbances such as hypokalemia or hypomagnesemia. The effects of aging on drug metabolism and excretion, may add to the risk of exposure to supratherapeutic drug concentrations (Kivelä and Räihä 2007; Danielsson et al. 2016). Older adults also have an impaired ability to compensate for adverse drug events (Kivelä and Räihä 2007).

As guidelines recommend that attention should be given especially to patients with higher risk of QT prolongation and TdP, these events should be considered when prescribing drugs (Royal College of Psychiatrists London 2006; Drew et al. 2010; Danielsson et al. 2016). Aging does not generally affect DDIs, but the likelihood of DDIs appearing in older adults increase due to the use of multiple drugs (Kivelä and Räihä 2007). Pharmacokinetic DDIs regarding QT prolongation, involving CYP enzymes (e.g. CYP3A4, CYP2D6) are to be avoided, as well as concomitant use of QT prolonging drugs (pharmacodynamic interaction; additive effect) (Kivelä and Räihä; INXBASE 2018). The ACC/AHA/ESC 2006 guidelines recommend that older adults with ventricular arrhythmias should generally receive the same treatment as younger adults (Zipes et al. 2006). Nonetheless, older adults receiving antiarrhythmic drugs should have the dosing and titration schedule adjusted to the altered pharmacokinetics of older adults. Risk assessment tools, especially those considering a wide range of patient-specific risk factors, such as risk scores for QT prolongation may be useful when contemplating QT prolonging pharmacotherapy in older adults.

7 SERVICES FOR OLDER ADULTS IN FINLAND

The Finnish health care system is undergoing a reform, however, at the moment the municipalities have the primarily responsibility for funding and organizing health care services, which are divided into primary care and specialized care services (Ministry of Social Affairs and Health 2018a,b). Health care services may be acquired from the public, private health care providers or the third sector by municipalities or individual residents. Private community pharmacies provide pharmaceutical services for outpatients. Municipalities are required to arrange and develop services to support the wellbeing,

health and functional capacity of older adults (Act on Supporting the Functional Capacity of the Older Population and on Social and Health Services for Older Persons 980/2012). The services should promote older adults to reside in their own homes independently or with assistance. Home care services consist of home help services and home nursing services (Ministry of Social Affairs and Health 2015). Clients receiving regular home care services in Finland were in November 2017 73,806 and of these 65% were female (National Institute for Health and Welfare 2018). The home care clientele increased by 0.4% since the year before. Of regular home care clients 77% were ≥75-year-olds.

Various health care providers may be involved in the implementation of patients' pharmacotherapy, such as practical nurses, registered nurses, physicians, pharmacists, as well as relatives (National Institute of Health and Welfare 2016b; Finnish Medicines Agency 2012). Home nursing services consist of medical care ordered by a physician, generally carried out by staff with an education in nursing (Ministry of Social Affairs and Health 2015; Ministry of Social Affairs and Health 2018b). Home help services are carried out by home aids, auxiliary nurses and licensed practical nurses. They tend to the clients' everyday needs as well as follow up their health status. Problems regarding social wellbeing and health as well as problems related to pharmacotherapy should be identified early and support should be given to the older adults (Act on Supporting the Functional Capacity of the Older Population and on Social and Health Services for Older Persons 980/2012). However, due to inadequate coordination of patient care and challenges in the implementation of interprofessional collaboration in pharmacotherapy management, DRPs may arise in home care clients (Kallio et al. 2016; Toivo et al. 2018b).

EMPIRICAL PART

8 OBJECTIVE

The main objective of the master's thesis was to study the prevalence of use of drugs associated with QT prolongation and TdP in older home care clients (≥65-year-olds). The study material (medication lists) was collected in fall of 2015 in Lohja, Finland (Toivo et al. 2018a,b). Concomitant use of drugs associated with QT prolongation and TdP was studied in the study participants. In addition, clinically significant DDIs (SFINX-D interactions) contributing to QT prolongation were studied. The secondary objective was to study the most commonly used QT prolonging drugs and which therapeutic class was associated with QT prolongation to the highest degree among the participants.

9 MATERIAL AND METHOD

The material used in the master's thesis originated from a randomized controlled trial (RCT) in Lohja, Finland, "Development of a Coordinated, Community-Based Medication Management Model for Home-Dwelling Aged in Primary Care" (Toivo et al. 2018a,b). In the master's thesis, the analysis of the material was only deepened regarding QT prolonging drugs. The collaborators of the RCT were University of Helsinki, Services for Aged People in City of Lohja and 1st Pharmacy of Lohja. The RCT was financed by the Social Insurance Institution (SII), Finland.

The participants of the RCT were older adults, (≥65-year-olds), receiving regular home care from the City of Lohja. Lohja Home Care Unit is divided into five service areas; Länsilohja, Mäntynummi, Nummentausta, Routio and Virkkala. In November 2015, 386 clients received home care in Lohja (National Institute for Health and Welfare 2016a). Nurses and practical nurses recruited clients to the RCT (Toivo et al. 2018b). A flow diagram of the study with timeline is shown in Figure 3. Of home care clients in Lohja, 191 clients agreed to the RCT and of these the medication lists of 188 clients were

available. The clients were randomized into an intervention group and a control group. The clients were randomized by home care service area, which each had its own nursing staff, to prevent contamination between the intervention group and the control group and subsequent dilution of the intervention. The intervention group (n=104) and control group (n=87) included clients from three and two home care service areas, respectively. The intervention group received the intervention in the first year of the RCT, a coordinated medication management model (CoMM) (Toivo et al. 2018b). The control group received standard care and subsequently the intervention after the first year. An automated dose dispensing service was used by about 90% of the participants.

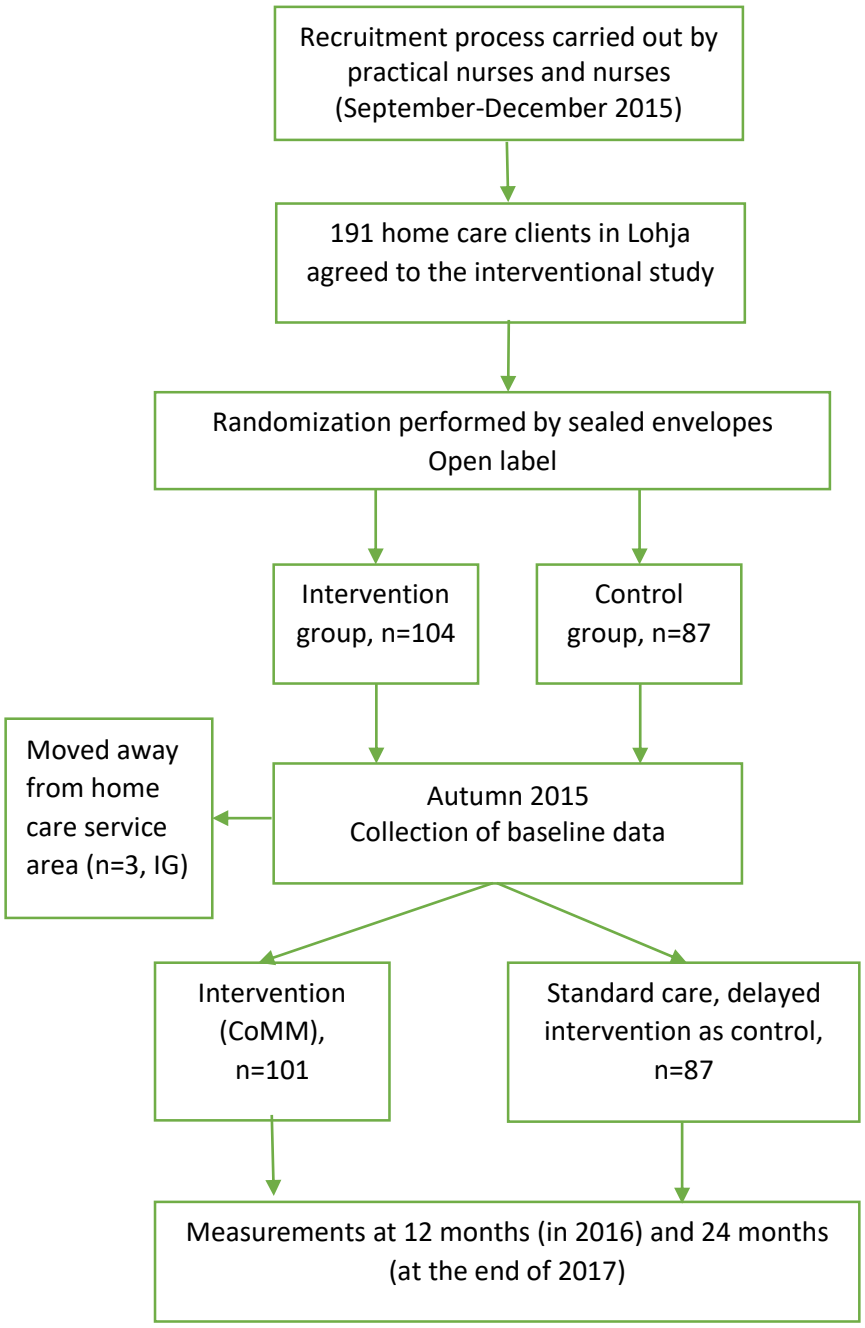

Figure 3. The randomized controlled trial in City of Lohja (Toivo et al. 2018b). IG = intervention group. CoMM = coordinated medication management model.

9.1 Baseline data

Information on the participants' (n=188) medications was updated by responsible nurses and printed from the electronic health record in fall of 2015. The participants' medications were reviewed with Salko and SFINX. Salko is a screening tool for finding potentially inappropriate medications in older adults (Suomen Apteekkarilehti 2012; Leikola 2013). From the Salko report, anticholinergic and serotonergic drugs as well as drugs according to Beer's criteria were documented individually. From the SFINX report, clinically significant DDIs (SFINX-D interactions) were documented.

The participants' regularly taken prescription drugs and pro re nata (PRN) drugs were reviewed. Where relevant, the drug's trade name, strength, pharmaceutical form, single dose and daily dose were available. Drugs were classified according to the anatomical therapeutic chemical (ATC) classification system (World Health Organization 2016). In the baseline data, combination products were recorded by active pharmaceutical ingredient (API) in cases of finding an individual ATC code. If an ATC code for the individual API was not found, the drug product was recorded using the ATC code of the combination product.

The cross-sectional baseline data did not contain other demographic data, nor lab results nor diagnoses. The frequency of used drugs was analyzed, and the participants were categorized according to the number of used drug; 1) 1-6, 2) 7-9, 3) 10-15 and >15 used drugs. The definition of polypharmacy was seven concomitantly used drugs in the master's thesis, as in the study by Jyrkkä 2017. The participants' age at the end of 2015 was determined by the year of birth in the participants' research ID. Mean age, standard deviation and distribution were calculated in four age categories. The participants' sex (female or male) and home care service area was also coded in a study number. A frequency distribution for the participants' sex was determined. Information on the intervention group and the control group were written into two different baseline data files.

9.2 Drugs associated with QT prolongation and TdP

In this master's thesis, parts of the cross-sectional baseline data from the RCT was used as the analysis of the material was only deepened regarding QT prolonging drugs. Relevant data included the participants' (n=188) study number which contained the participants' age, sex and home care service area, and medication lists. Background information of the participants and the frequency of used drugs were taken from the master's thesis of Jyrkkä 2017.

The participants' regularly taken drugs and PRN prescription drugs were analyzed regarding drugs associated with QT prolongation and TdP. AZCERT's CredibleMeds was used for identifying drugs associated with QT prolongation and TdP (Woosley et al. 2018b). QTDrugs Lists 1-3 of CredibleMeds were modified and a Microsoft® Excel® file containing drugs with risk of QT prolongation and TdP found on the Finnish market was created. Finnish Medicines Agency's FimeaWeb was used for finding drugs available in Finland (Finnish Medicines Agency 2017). Drugs with known risk (QTDrugs List 1), possible risk (QTDrugs List 2) and conditional risk (QTDrugs List 3) of TdP were placed into separate worksheet tabs in the Microsoft® Excel® file.

A pre-analysis plan was created, containing information on which QTDrugs List was to be used in the analysis of prevalence of use of QT prolonging drugs in the participants, in the analysis of concomitant use of QT prolonging drugs and in the analysis of the most commonly used QT prolonging drugs. The Microsoft® Excel® file containing drugs associated with QT prolongation and TdP as well as the participants' medication lists were used in cross-tabulation analysis performed by a statistician. Additionally, the author analyzed the SFINX report, in order to find DDIs contributing to QT prolongation and TdP.

9.3 Statistical analysis

The data was analyzed quantitatively using SAS® (SAS Institute Inc.) and Microsoft® Excel® (Microsoft Corporation). The intervention group and the control group were

analyzed separately and combined. A comparison between the intervention group and the control group and the difference between them was tested statistically. The distribution of variables was described as frequencies (n) and relative frequencies (%). For describing the central tendency, the mean and median was used when the data was normally distributed and skewed, respectively. The normal distribution of variables was tested with Kolmogorov−Smirnov test. Standard deviation and range were used as measures of dispersion. Cross-tabulation was used for comparison of the intervention group and the control group. The difference between them was tested with Chi-Square test. Fisher's exact test was used when Chi-Square test did not meet the preconditions. The difference in mean values between the groups was tested with t-test. If conditions for the test were not met and the variable was at least of ordinal scale, Mann-Whitney U test was performed. A p-value ≤ 0.05 was considered significant in this study. The statistician of the RCT aided in the statistical analysis according to the pre-analysis plan.

10 ETHICAL ASPECTS OF THE STUDY

The research permit for the RCT was granted by City of Lohja. The RCT had a favorable statement from the Coordinating Ethics Committee of The Hospital District of Helsinki and Uusimaa (number 153/13/03/00/15). The RCT was registered in ClinicalTrials.gov (NCT02545257) (Toivo et al. 2018a). A person familiar with the RCT was responsible for informing (both orally and in writing) the participants of the RCT. Participation in the study was voluntary and if desired, the participant could withdraw from the study. Written informed consent was given by the participant or their closest proxy. The baseline data contained a study number for each participant, to keep the participants anonymous.

The master’s thesis was conducted in accordance with the responsible conduct of research (RCR) guidelines (Finnish Advisory Board on Research Integrity 2013). A separate ethical statement from an ethical review committee was not necessary for this master’s thesis since no new material was gathered. Neither was a separate research permit. When receiving the baseline data for the study, a data release consent form was signed and returned to Terhi Toivo, main supervisor of this master’s thesis and project coordinator

of the RCT. All material received for this master's thesis was handled confidentially. At completion of the master's thesis, the received material was returned, and deleted from the author's workstation.

11 RESULTS

11.1 Participants

The participants (n=188) of the RCT were home care clients residing in Lohja, (≥65-year-olds). The participants were randomized into an intervention group (n=101) and control group (n=87). The majority (69%) of the participants were women (Table 10) (Jyrkkä 2017). The mean age of the participants was 83 years. Of the participants, 44% were at least 85-year-olds. The second largest age group was 80-84-year-olds. There was no statistically significant difference between the intervention group and the control group regarding age distribution.

Table 10. Background information of participants (n=188) (Jyrkkä 2017).

	Total (n=188)	**Intervention group (n=101)**	**Control group (n=87)**	**p-value[1]**
Age (years)	**n (%)**	**n (%)**	**n (%)**	0.075
65-69	9 (5)	5 (5)	4 (5)	
70-74	14 (7)	7 (7)	7 (8)	
75-79	27 (14.4)	21 (21)	6 (7)	
80-84	55 (29.3)	30 (30)	25 (29)	
>85	83 (44)	38 (38)	45 (52)	
Age (years) Mean (SD[2])	83.1 (6.91)	82.5 (6.95)	83.7 (6.83)	
Sex	**n (%)**	**n (%)**	**n (%)**	0.298
Female	129 (69)	66 (65)	63 (72)	
Male	59 (31)	35 (35)	24 (28)	

[1] Chi-Square test
[2] Standard deviation

11.2 Frequency of used drugs

The mean number of regularly taken drugs and PRN drugs used by the participants was 13 (SD 4.5, range 3-31) (Jyrkkä 2017). Four participants out of five (79%) used at least 10 drugs (Table 11). Polypharmacy was found in 94% of the participants, when the definition of polypharmacy was seven concomitantly used drugs.

Table 11. Regularly taken drugs and pro re nata drugs used by the participants (Jyrkkä 2017).

	Total (n=188)		**Intervention group (n=101)**		**Control group (n=87)**		**p-value[1]**
Frequency of used drugs[a]	**n**	**%**	**n**	**%**	**n**	**%**	0.377
1-6	12	6	4	4	8	9	
7-9	27	14	14	14	13	15	
10-15	105	56	61	60	44	51	
>15	44	23	22	22	22	25	
Mean (SD[b])	12.8 (4.5)		13.0 (4.4)		12.6 (5)		0.700[2]

[1] Chi-Square test
[2] Mann−Whitney U-test
[a] Contains both regularly taken drugs and pro re nata drugs
[b] Standard deviation

11.3 Drugs associated with QT prolongation and TdP

Table 12 shows the prevalence of use of drugs associated with QT prolongation and TdP in the participants (n=188). On average, the participants (n=188) used 2.3 drugs (SD 1.3, median 2.0) associated with QT prolongation and TdP. There was no statistically significant difference between the intervention group and the control group regarding the prevalence of use of QT prolonging drugs.

Of the participants, 36% (n=67) used drugs with known risk of TdP (CredibleMeds QTDrugs List 1). On average, the participants (n=188) used 0.4 drugs (SD 0.56) with known risk of TdP.

The prevalence of CredibleMeds QTDrugs List 2 drug use was 36% (n=67). On average, the participants (n=188) used 0.5 drugs (SD 0.73) with possible risk of TdP.

Most of the participants (n=156, 83%) used drugs that under certain circumstances are associated with TdP (CredibleMeds QTDrugs List 3). On average, the participants (n=188) used 1.5 drugs (SD 1.0, median 1.0) with conditional risk of TdP.

Table 12. Number of participants using drugs associated with QT prolongation and torsades de pointes (according to CredibleMeds QTDrugs Lists [Woosley et al. 2018b]).

	Total (n=188)		**Intervention group (n=101)**		**Control group (n=87)**		**Intervention vs control group**
	n	**%**	**n**	**%**	**n**	**%**	**p value[1]**
Drugs with known risk of TdP (QTDrugs List 1)[a]	67	36	34	34	33	38	0.542
Drugs with possible risk of TdP (QTDrugs List 2)[b]	67	36	33	33	34	39	0.360
Drugs with conditional risk of TdP (QTDrugs List 3)[c]	156	83	84	83	72	83	0.940

[1] Chi-Square test

QTDrugs Lists of AZCERT's CredibleMeds.org (Woosley et al. 2018b).

[a] QTDrugs List 1 - contains drugs that prolong the QT interval and are known for their risk of TdP, even when taken as recommended

[b] QTDrugs List 2 - contains drugs that may cause QT prolongation but there is a lack of evidence of TdP risk when taken as recommended

[c] QTDrugs List 3 - contains drugs that under certain circumstances are associated with TdP (e.g. hypokalemia, excessive dose, drug-drug interactions)

11.4 Concomitant use of drugs associated with QT prolongation

Concomitant use of drugs with known and possible risk of TdP (QTDrugs Lists 1 and 2) was analyzed (Table 13). One fifth of the participants used concomitantly 2-3 drugs associated with QT prolongation and TdP. A small fraction of the participants used concomitantly ≥4 drugs associated with QT prolongation and TdP.

Table 13. Number of participants using concomitant drugs which are associated with QT prolongation and torsades de pointes.

	Total (n=188)		Intervention group (n=101)		Control group (n=87)		Intervention vs control group
Concomitant use of drugs associated with QT prolongation[a]	**n**	**%**	**n**	**%**	**n**	**%**	**p value[1]** 0.0596
2-3	40	21	17	17	23	26	
≥4	2	1	0	0	2	2	

[1] Fisher's Exact Test

[a] Regularly taken drugs and pro re nata drugs. Drugs found on QTDrugs Lists 1 and 2 analyzed.

11.5 Most commonly used drugs associated with QT prolongation and torsades de pointes (QTDrugs Lists 1-3)

Eight drugs (8 ATC codes) with known risk of TdP (QTDrugs List 1) was found in the participants' (n=188) medication lists (Table 14). Psychoanaleptics (ATC code N06, including antidepressants, psychostimulants, anti-dementia drugs and psycholeptics and psychoanaleptics in combination) was the most commonly used drug class, with three of the eight drugs belonging to this drug class. Donepezil was the most commonly used drug with known risk of TdP, n=26.

Table 14. Most commonly used drugs with possible risk of TdP (drugs found on QTDrugs List 1).

	Total (n=188)
Drugs with known risk of TdP	**n (%)**
Donepezil	26 (14)
Citalopram	24 (13)
Escitalopram	7 (4)
Haloperidol	4 (2)
Levomepromazine	4 (2)
Sotalol	4 (2)
Amiodarone	3 (2)
Ondansetron	2 (1)

Thirteen drugs (13 ATC codes) with possible risk of TdP (QTDrugs List 2) was found in the participants' (n=188) medication lists. The most commonly used drug with possible risk of TdP (found on QTDrugs List 2) was the opioid buprenorphine, n=28 (Table 15). Two of the most commonly used drugs with possible risk of TdP were antidepressants (mirtazapine and venlafaxine).

Table 15. Most commonly used drugs with possible risk of TdP (drugs found on QTDrugs List 2).

	Total (n=188)
Most commonly used drugs with possible risk of TdP	**n (%)**
Buprenorphine	28 (15)
Mirtazapine	16 (9)
Risperidone	15 (8)
Tramadol	9 (5)
Venlafaxine	6 (3)

The most commonly used drug with conditional risk of TdP (QTDrugs List 3) was the diuretic furosemide, n=104 (Table 16). Another diuretic, hydrochlorothiazide, was found, while the other drugs in the top five of the most commonly used list 3 drugs were proton pump inhibitors. Nineteen drugs (19 ATC codes) with conditional risk of TdP was found in the participants' (n=188) medication lists.

Table 16. Most commonly used drugs with conditional risk of TdP (drugs found on QTDrugs List 3).

	Total (n=188)
Most commonly used drugs with conditional risk of TdP	**n (%)**
Furosemide	104 (55)
Pantoprazole	61 (32)
Hydrochlorothiazide	18 (10)
Esomeprazole	14 (7)
Omeprazole	14 (7)

11.6 QT prolonging drug-drug interactions

Clinically significant DDIs (SFINX-D interactions) were analyzed. QT prolonging DDIs were found in 5 (3%) participants (Table 17). The drugs involved in the QT prolonging DDIs belonged to the drug classes psychoanaleptics and psycholeptics.

Table 17. SFINX class D drug-drug interactions contributing to QT prolongation and drugs causing the interactions. The mechanism and prevalence in the intervention (n=101) and control groups (n=87). (INXBASE 2018).

Drugs	SFINX class	Mechanism	Intervention group, n	Control group, n
Citalopram–Donepezil (QTDrugs List 1 drugs)	D0	Additive prolonging effect on the QT interval	2	1
Escitalopram– Donepezil (QTDrugs List 1 drugs)	D0	Additive prolonging effect on the QT interval	1	
Citalopram–Haloperidol (QTDrugs List 1 drugs)	D1	Additive prolonging effect on the QT interval		1

11.7 Risk factors for QT prolongation and torsades de pointes

Table 18 summarizes the risk factors found in the participants. Donepezil, (es)citalopram and haloperidol (QTDrugs Lists 1 drugs) were drugs associated with the highest risk of QT prolongation and TdP in the participants. Drugs listed on the QTDrugs Lists 2-3 (possible and conditional risk of TdP) but associated with a lower risk of QT prolongation and TdP in these participants, could not be clearly identified.

Table 18. Risk factors found in the participants.

Risk factors	**Total (n=188) n (%)**
Drugs with known risk of TdP (QTDrugs List 1)	67 (36)
(Es)citalopram	31 (16)
Donepezil	26 (14)
Haloperidol	4 (2)
Drugs with possible risk of TdP (QTDrugs List 2)	67 (36)
Drugs with conditional risk of TdP (QTDrugs List 3)	156 (83)
Age ≥65 years	188 (100)
Female sex	129 (69)

12 DISCUSSION

12.1 Non-pharmacological risk factors

This study investigated drugs associated with QT prolongation and TdP in older adults receiving home care (n=188) in City of Lohja. The prevalence of risk factors for QT prolongation and TdP has not been widely studied in outpatients since there is overall a shortage of studies conducted in outpatients using QT prolonging drugs, especially in Finland. However, it is known that older adults have an increased risk of QT prolongation and TdP as the prevalence of risk factors such as multiple illnesses, electrolyte disturbances and use of multiple drugs increase in these people (Drew et al. 2010; Moreno-Gutiérrez et al. 2016).

In the present study, several risk factors commonly found in outpatients in other studies were also found in a large part of the participants. In this study, all the participants were ≥65-year-olds. It is known that the QT interval increase with older age (Rabkin 2015; Woosley et al. 2018c). Additionally, almost 70% of the participants were of female sex, which is another risk factor for QT prolongation (Woosley et al. 2018c).

In a German study in patients with LQTS and TdP, 60% of the patients had developed the conditions in outpatient settings (Sarganas et al. 2014). Forty percent of the patients were ≥65 years and 66% were women. The two most common non-pharmacological risk

factors besides female sex and age in this study was hypokalemia (53% of the patients) and renal dysfunction (26% of the patients). Renal function declines with age, which also can be expected in the participants of the RCT, although lab result data of the participants were not available for the present study (Kivelä and Räihä 2007). In a large Colombian study in outpatients, 97% had at least one risk factor, excluding female sex and higher age (Moreno-Gutiérrez et al. 2016). Three risk factors for TdP was found in 64% of the participants. In a recent systematic review on case reports on drug-induced TdP, it was found that almost 35% (21 patients) had modifiable risk factors for TdP (Jackobson et al. 2018). The most prevalent modifiable risk factor was hypokalemia. Of non-modifiable risk factors (found in 89% of the patients), the most common were found to be female sex and congestive heart failure. Both modifiable and non-modifiable risk factors were found in 28% of the cases of drug-induced TdP. For assessing the risk of QT prolongation and TdP, several risk assessment tools have been developed, e.g. risk scores, and a few of them have been further implemented in CDSSs (Haugaa et al. 2013; Tisdale et al. 2013; Tisdale et al. 2014; Vandael et al. 2017a). Using risk assessment tools, patients' modifiable risk factors may be reduced, and actual events of QT prolongation and TdP may be avoided.

12.2 Prevalence of use of drugs associated with QT prolongation and TdP

Of the two types of LQTS, aLQTS is the more common one and QT prolonging drugs are responsible for a significant part of cases of QT prolongation (van Noord et al. 2010; Laksman et al. 2015). In this study, the participants' regularly taken drugs and PRN drugs were analyzed regarding drugs associated with QT prolongation and TdP. CredibleMeds' QTDrugs Lists were used for identifying drugs associated with QT prolongation and TdP (Woosley et al. 2018b). Of the QTDrugs Lists, List 1 and 2 are clinically relevant as these contain drugs that are known for their risk of TdP as well as drugs that have a possibility of causing TdP.

The mean number of regularly taken drugs and PRN drugs used by the participants was 13 (SD 4.5, range 3-31) (Jyrkkä 2017). The mean number of drugs used by the participants in this study was 13, indicating polypharmacy in the participants, which adds

to the risk of QT prolongation and TdP. Polypharmacy was found in the majority of the participants (94%), meaning that there may be an increased risk of QT prolongation and TdP in these patients. However, in this study the definition of polypharmacy was seven concomitantly used drugs, when the definition of polypharmacy in many studies has been the use of 5 drugs. On average, the participants used 2.3 drugs (SD 1.3, median 2.0) associated with QT prolongation and TdP. This is a slightly higher number than in the study in older outpatients conducted in the Republic of Colombia (Moreno-Gutiérrez et al. 2016). In the study, participants used a mean of 1.12 (SD 0.35, range 1-5) drugs of the QTDrugs Lists of CredibleMeds.

Of the Colombian outpatients, about 95% used drugs that under certain circumstances are associated with TdP (QTDrugs List 3) (Moreno-Gutiérrez et al. 2016). These circumstances may be occurrence of electrolyte disturbances and DDIs and use of excessive dose (Woosley et al. 201). Likewise, most of the older adults receiving home care in Lohja (83%) used drugs with conditional risk of TdP (QTDrugs List 3). In older adults with multiple illnesses, the use of diuretics, of which a few have a conditional risk of TdP, is common (Statens beredning för medicinsk och social utvärdering 2009; Woosley et al. 2018b). In both the Colombian study and the present study, the diuretics furosemide and hydrochlorothiazide were commonly used by a large part of the participants. The use of diuretics in older adults should be closely monitored as diuretics are associated with electrolyte disturbances, such as hypokalemia and hypomagnesemia and even congestive heart failure (Drew et al. 2010). Additionally, some diuretics may block potassium currents, reducing the repolarization reserve.

Drugs with known risk of TdP was used by 36% of the participants in this RCT. The prevalence of use of QTDrugs List 1 drugs was higher in this study than in studies in outpatients conducted in the Republic of Colombia (5.3%) and Germany (17.3%) (Moreno-Gutiérrez et al. 2016; Schächtele et al. 2016). This may be partially explained by the higher mean number of drugs used by the participants in the present study. The participants were older adults in need of regular home care services, i.e. the participants had poorer functional capacity than independently functioning older adults. They may also have been more medicated than independently functioning older adults. Prescribers

and pharmacists may not have extensive knowledge of QT prolonging drugs or be able to assess the risk of QT prolongation and TdP in older adults.

The most commonly used drug class with known risk of TdP in the present study was psychoanaleptics. Donepezil and citalopram were the most commonly used drugs. Citalopram was also the most commonly used drug with known risk of TdP in the study by Schächtele et al. (2016). The use of antidepressants and antipsychotics in older adults have increased in Finland, as well as internationally, in the last decade (Charlesworth et al. 2015; Saastamoinen and Kurko 2016). Changed attitudes towards mental health as well as introduction to newer antidepressants may explain the increase in antidepressant use (Charlesworth et al. 2015). Selective serotonin reuptake inhibitors (SSRIs) such as citalopram are considered relatively safe in older adults (Kivelä and Räihä 2007; Wiese 2011). However, use of citalopram and escitalopram is associated with a dose-dependent increase in the risk of QT prolongation (European Medicines Agency 2011; Oy H. Lundbeck Ab 2011). In a Swedish case-control register study conducted in older adults dying outside hospitals in 2008-2013, it was found that citalopram was the most commonly prescribed antidepressant (44% of prescriptions) and was associated with a high adjusted hazard ratio for death (HR=1.6) (Danielsson et al. 2016). Due to reevaluation and review of QT studies, the recommended dose of (es)citalopram was lowered in older adults a few years ago. The recommended maximum dose of citalopram and escitalopram for older adults (≥65-year-olds) is 20 mg and 10 mg daily, respectively (European Medicines Agency 2011; Oy H. Lundbeck Ab 2011).

Compared with previous studies, drugs with possible risk of TdP was used by a greater percentage of the participants in the present study (36%). Of drugs with possible risk of TdP, the most commonly used drugs in the present study were psychoanaleptics, such as mirtazapine and venlafaxine and opioid analgesics. Indication for pharmacological treatment was not available for the present study. Psychoanaleptics and psycholeptics, more specifically antidepressant and antipsychotics are often used without any precise indication for treatment (Skoog et al. 2015). In a large Swedish cross-sectional study in older adults it was found that 40% of patients using SSRIs had indication for these drugs and 18% of the patients using antipsychotic drugs had indication. The estimated rates of

inappropriate prescribing of these types of drugs may be partially explained by off-label prescribing. Additionally, drugs may be used needlessly for an extended period, i.e. drugs that no longer are indicated or appropriate are not deprescribed. The results of the studies by Skoog et al. (2015) and Danielsson et al. (2016) accentuate that psychoanaleptics and psycholeptics should be prescribed to older adults exclusively when there is an appropriate indication. The risk and benefit of the pharmacological treatment should be assessed individually and with taking the altered pharmacokinetics of older adults into consideration.

12.3 Concomitant use of QT prolonging drugs

In this present study, concomitant use of drugs with known risk and possible risk of TdP (QTDrugs Lists 1 and 2) was investigated. One fifth of the participants (n=188) used concomitantly 2-3 drugs associated with QT prolongation and TdP. The use of ≥4 drugs associated with QT prolongation and TdP was only found in the control group, however the difference between the groups was not statistically significant. The findings in this study are similar to those from previous studies conducted in outpatients. However, concomitant use of QT prolonging drugs found on the QTDrugs Lists of CredibleMeds have been investigated in slightly different ways in previous studies. In the study by Moreno-Gutiérrez et al. 2016, ≥2 QT prolonging drugs (QTDrugs List 1-3) were used by 10% of the patients. Schächtele et al. (2016) investigated additional use of QT prolonging drugs of any risk category in patients using at least 1 drug with known risk of TdP (QTDrugs List 1). Concomitant use of 2 QT prolonging drugs was found in 38% of the participants. Of the participants, 14% used 3 QT prolonging drugs and 4% used at least 4 QT prolonging drugs.

Simultaneous prescribing of QT prolonging drugs is to be avoided in older adults (Kivelä and Räihä 2007; Jackobson et al. 2018). Nevertheless, it appears that concomitant use of QT prolonging drugs is common and has increased in inpatients as well as outpatients (Curtis et al. 2003; Sarganas et al. 2014; Tay et al. 2014; Moreno-Gutiérrez et al. 2016; Schächtele et al. 2016). The frequent concomitant prescribing of QT prolonging drugs brings into question whether prescribers have judged the risks of concomitant use of QT

prolonging drugs to be clinically insignificant or if their knowledge of the risks of QT prolonging drugs is inadequate.

12.4 Drug-drug interactions

Clinically significant DDIs (SFINX-D interactions) contributing to QT prolongation were found in 3% of participants. All were pharmacodynamic DDIs and involved QTDrugs List 1 drugs. The most commonly occurring interaction in this study was the concomitant use of citalopram/escitalopram and donepezil. Donepezil was added to QTDrugs List 1 in 2015, which may be why the interaction was not recognized in the RCT. INXBASE (SFINX) uses the QTDrugs Lists of CredibleMeds as one reference for QT prolonging drugs (INXBASE 2018). A recent study in Sweden also used this DDI database in their study, however in Sweden it goes by another name, Janusmed interaction database. Citalopram-donepezil was the most common D interaction in this study in older adults with dementia admitted to two hospitals in Northern Sweden (Sönnerstam et al. 2018). Based on clinical experience, antidepressant therapy may be appropriate in dementia patients with moderate to severe depression (Memory Disorders. Current Care Guidelines 2017). Citalopram is commonly prescribed to treat depression in older adults with dementia as citalopram is seen to have less clinically relevant interactions than other SSRIs (Kivelä and Räihä 2007; Sönnerstam et al. 2018). If concomitant use of these drugs is inevitable, ECG monitoring and following up QTc is recommended (INXBASE 2018). Additionally, the patient's other risk factors should be assessed.

12.5 Validity and reliability of the study

This study primarily investigated the prevalence of use of drugs associated with QT prolongation and TdP and concomitant use of such drugs in home care clients (n=188), using their medication lists. Parts of the cross-sectional baseline data from the original RCT was used as the analysis of the material was only deepened regarding QT prolonging drugs. The participants were divided into an intervention group (n=101) and a control group (n=87). Randomization of the RCT was successful when comparing the

participants' background information and use of drugs in the intervention group and control group. The number of participants was moderate.

The medication lists were updated by nurses before the starting point of the RCT, making the medication lists reliable sources. Additionally, most of the participants used a dose dispensing service, which requires an updated medication list. Both regularly taken prescription drugs as well as PRN prescription drugs were taken into account in this study. The dosing regimen was not considered, which might have slightly overestimated the prevalence of use of QT prolonging drugs in the participants. QT prolongation and TdP may appear in a dose-dependent manner (Drew et al. 2010; Tisdale 2016). SFINX-C interactions could possibly have been investigated in this study. SFINX-C interactions are also clinically relevant interactions in older adults and may be managed with e.g. dose adjustments. However, since doses were not investigated in this study, the focus remained on SFINX-D interactions, which are clinically relevant DDIs best avoided.

This study comes with the limitation that the cross-sectional baseline data did not included demographic data, diagnoses, lab results nor ECG measurements. Information on the duration of the participants' pharmacotherapy was not available due to the research method and cross-sectional design. Drugs actually used by the participants was not ensured as the participants were not interviewed. The participant's state of health was not ensured with interviews. Other heart-related DDIs or pharmacotherapy that may lead to electrolyte disturbances were not assessed. This means that the present study could not fully assess the risk of QT prolongation and TdP in the participants. Clinical outcomes such as occurrence of QT prolongation or TdP could not either be measured.

The reliability of the study improved by careful planning of the analysis together with people of the research team of the RCT. The reliability of the results improved by having the interventional study's IT expert conduct the statistical analysis, according to a pre-analysis plan.

Drugs were classified according to the ATC classification system, improving the comparability. For identification of drugs associated with QT prolongation and TdP, the

QTDrugs Lists of CredibleMeds were used. These QTDrugs Lists are regularly updated and the author received notifications on which drugs had been added to the lists during the planning of the master's thesis. Drugs on the QTDrugs Lists were cross-referenced with Finnish Medicines Agency's FimeaWeb search, creating an updated list of QT prolonging drugs available in Finland. There is no officially approved list of QT prolonging drugs in Finland, neither is there in most other countries. CredibleMeds is a helpful website for identifying clinically relevant drugs associated with QT prolongation and TdP as drugs are categorized into four TdP risk categories based on ongoing systematic research and it is the only tool of its kind. Recently a list of risk factors for QT prolongation and TdP was released on the CredibleMeds website, adding to the usefulness of the website.

In the analysis, only QT prolonging drugs recognized on the CredibleMeds website were considered, meaning that drugs marketed in the USA were taken into account. Warnings of QT prolongation and TdP on the QTDrugs Lists may differ from warning in summaries of product characteristics. For identification of QT prolonging DDIs in this study, INXBASE (SFINX) was used. The risk assessment tools INXBASE and RISKBASE use CredibleMeds as a reference, however the tools and the QTDrugs Lists do not necessarily agree on which drugs with risk of QT prolongation and TdP are clinically relevant (IXBASE 2018). Harmonization of risk assessment tools is desired.

12.6 Generalizability and applicability of the results

This study investigated the use of drugs associated with QT prolongation and TdP in older adults receiving home care in City of Lohja. The results show that a large part of the home care clients was prescribed drugs associated with QT prolongation and TdP. Polypharmacy was found in the majority of the participants. The results are generalizable to a certain degree as prescribing practices and health care professionals' knowledge of QT prolongation and TdP may vary between cities and municipalities. Additionally, as remote medical consultations may be used in some home care services areas, the aforementioned aspects may vary (Laitila 2015).

TdP is one of the most widely studied and recognized adverse drug events in inpatients (Schwartz and Woosley 2016). Therefore, this drug-related problem should be preventable. As seen in this master's thesis, there is a lack of studies conducted in outpatients and especially in older adults, who have an increased risk of QT prolongation and TdP. For many health care professionals, such as general practitioners, pharmacists and nurses, QT prolongation is still a new topic. This study sheds light on the fact that health care professionals need to be educated on how QT prolongation and TdP manifests themselves.

Recognizing risk factors and drugs that may prolong the QT interval is critical in the management of the DRP, which this thesis may assist with. There are no specific guidelines for the management of QT prolongation and TdP in outpatients published in Finland, or elsewhere for that matter. There is a need for systematic procedures for assessing and managing the risk of QT prolongation and TdP in the Finnish health care system.

A few databases and tools that may assist in assessing the risk of QT prolongation and TdP have been mentioned in this thesis, of which two have been developed partially by Finns. A wider use of risk assessment tools for QT prolongation and TdP is desired, as well as further development of already existing ones. The risk assessment tools also need to be integrated to fit several health information systems. Something to keep in mind when using and developing tools is the risk of alert fatigue. Although physicians may override alerts due to clinical circumstances, risk assessment tools need to be designed with increased sensitivity and specificity and they need to be evaluated regarding unnecessary generated signals. Pharmacists have an important role in ensuring that the pharmacotherapy of patients is safe, with the help of risk assessment tools and their education and knowledge. They also have an important role in communicating concerns regarding the safety of patients' pharmacotherapy to prescribers. Nurses and practical nurses have an important role in assessing the state of health of patients as well as identifying clinically significant DRPs. Increased collaboration between health care professionals and further defining the tasks and responsibilities of various health care professionals are essential for improving the patient safety.

12.7 Further research

Further efforts are needed to obtain more accurate knowledge of outpatients', especially home care clients' risks of QT prolongation and TdP. Further prospective research could focus on the clinical outcomes related to the use of QT prolonging drugs, e.g. incidence of TdP, hospitalization rates and mortality in older adults receiving home care. Developing risk assessment tools and improving the validity and reliability of already existing tools could be upcoming research topics. For example, the risk assessment tool RISKBASE could be explored in future studies. Furthermore, there is a need for studies investigating health care professionals' awareness and knowledge of QT prolongation and TdP and how health care professionals may prevent these DRPs.

13 CONCLUSIONS

There is a lack of studies investigating QT prolongation and TdP in outpatients. This is the first study conducted in Finland investigating the prevalence of use of QT prolonging drugs in older adults receiving home care. The prevalence of use of clinically relevant QT prolonging drugs (QTDrugs Lists 1-2 of CredibleMeds) was higher in this study compared with the prevalence in outpatients in previous studies. The majority of the participants in this study used drugs with conditional risk of TdP (QTDrugs List 3). Moreover, concomitant use of QT prolonging drugs is common in outpatients. For identification of clinically relevant drugs associated with QT prolongation and TdP, CredibleMeds is a helpful website.

Clinically significant DDIs (SFINX-D) was found in a small fraction of the older adults receiving home care in City of Lohja. The only known risk factors for QT prolongation and TdP in the home care clients of this study was the modifiable risk factor QT prolonging pharmacotherapy and the non-modifiable risk factors female sex and higher age. Older adults have an increased risk of QT prolongation and TdP due to modifiable and non-modifiable risk factors that are likely to occur with increased age; illness, pharmacotherapy and altered pharmacokinetics. Therefore, using risk assessment tools,

such as risk scores and DDI databases, patients' modifiable risk factors may be reduced, and actual events of QT prolongation and TdP may be avoided.

Health care professionals need be educated on the risks of QT prolongation and TdP and the risks of concomitantly prescribed QT prolonging drugs. In the management of QT prolongation and TdP it is critical to be aware of which drugs prolong the QT interval and cause TdP as well as recognize risk factors for QT prolongation and TdP. There is a need for systematic procedures for assessing and managing the risk of QT prolongation and TdP in the Finnish health care system.

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